

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

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PROTECTION AND ADSORPTION

'Pectocel' (Pectin and Kaolin Compound, Lilly) is a nonchalky kaolin mixture with a creamy, heavy-bodied smoothness. The ample kaolin contained in this preparation functions as an adsorptive and effectively produces a protective coating that soothes inflamed intestinal mucosa. The pleasant flavor and appearance of 'Pectocel' assure ready acceptance by the patient.

'Pectocel' is indicated for the supportive treatment of diarrhea and inflammation associated with enteritis, gastritis, colitis, and other intestinal infections or intoxications.

Formula

An aromatized aqueous suspension containing in one fluid ounce:

Pectin	4 1/2 grs.
Kaolin	90 grs.
Zinc Phenolsulfonate	1 1/8 grs.

Dose

One to four tablespoonfuls as often as indicated by the severity of the condition.

'Pectocel' is available at pharmacies everywhere.

P E C T O C E L

ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA, U. S. A.

I WANT MORE PABLUM!



EVANSVILLE, INDIANA, U.S.A.

Value of Meat and Vegetables in Baby Diets

EXCERPT:

"HOW TO RAISE A HEALTHY BABY"

Complete Information from Birth to the Sixth Year

by L. J. Halpern, B.S., M.D., F.A.A.P.

Prentice Hall, Inc., New York, 1940

Since there are so many vegetables that are good for infants, it is well to give a wide variety . . . [Strained] liver soup, especially made for infant feeding . . . contains not only various vegetables but also liver, which is valuable for its rich iron content. Page 132

EXCERPT:

"INFANT NUTRITION"

by P. C. Jeans, A.B., M.D., and Williams McKim Marriott, B.S., M.D.

The C. V. Mosby Company—Fourth Edition 1947

Vegetables should have an important place in the diet after the first few months of infancy. Page 243

Several of the prepared baby soups sold contain finely divided meat. Some of these are known as vegetable soups with cereal and meat . . . Page 245

Protein digestion and absorption during infancy are remarkably complete . . . Page 138

Campbell's Baby Foods Contain Both Meat and Vegetables



Campbell's baby foods are scientifically balanced mixtures of meat-and-vegetables.

This fact makes it simple to feed a baby important meat and vegetables as a single food.

There are four of these highly nutritious meat-and-vegetable mixtures:

CHICKEN	+ 5 VEGETABLES + SEMOLINA
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LIVER	+ 7 VEGETABLES + OATMEAL

—excellent as the meat-and-vegetable main course of a baby's meal.

A fifth soup—Vegetable—consists of 8 vegetables with oatmeal—suggested for the meal that is supplemented by an egg.

All five foods are strained. A baby may be started on them as early as any strained food.

They help assure adequate meat and vegetables through an infant's pre-molar months. For later on, blended with milk, they may be served as soups.

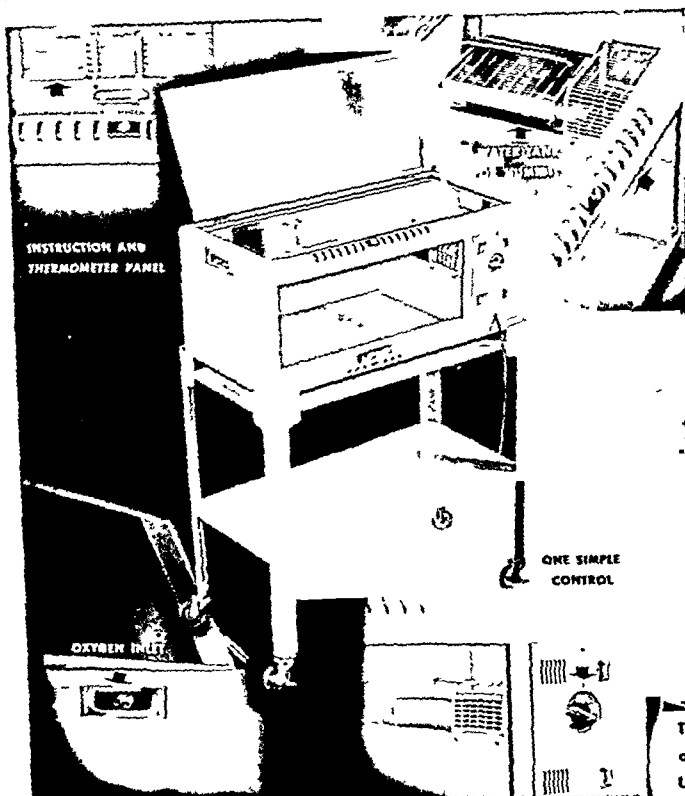
Packed in glass jars. Require warming only.

Campbell's
**STRAINED MEAT-AND-VEGETABLE
BABY SOUPS**

Dietetic analyses of these strained foods will be sent to any doctor upon request.

Every grocer who sells Campbell's Soups can supply Campbell's meat-and-vegetable Baby Soups

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1. Low cost
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9. Fireproof construction
10. Excellent oxygen tent
11. Welded steel construction
12. 3-ply safety glass
13. Full length view of baby
14. Simple outside oxygen connection
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The Armstrong X-4 Baby Incubator is the only Baby Incubator tested and approved by Underwriters' Laboratories for use with oxygen.

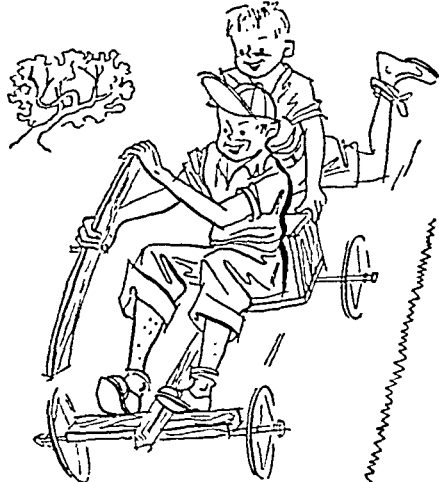
● In offering you the Armstrong X-4 Portable Baby Incubator we stand firmly on the principle that we must provide a **SAFE** Baby Incubator, a **LOW COST** Baby Incubator and a **SIMPLE** Baby Incubator.

That we have succeeded is evidenced by the fact that to date close to 400 Hospitals have placed voluntary repeat orders for more than 1200 additional Incubators. More and more it is being used, not only for the premature baby, but for any debilitated or under weight baby.

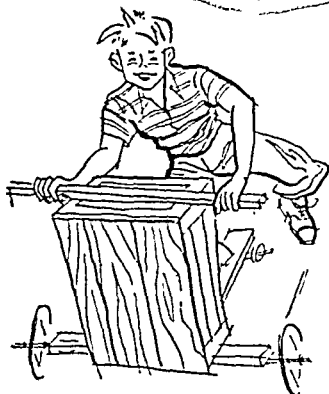
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equal opportunities *for the child with petit mal!*



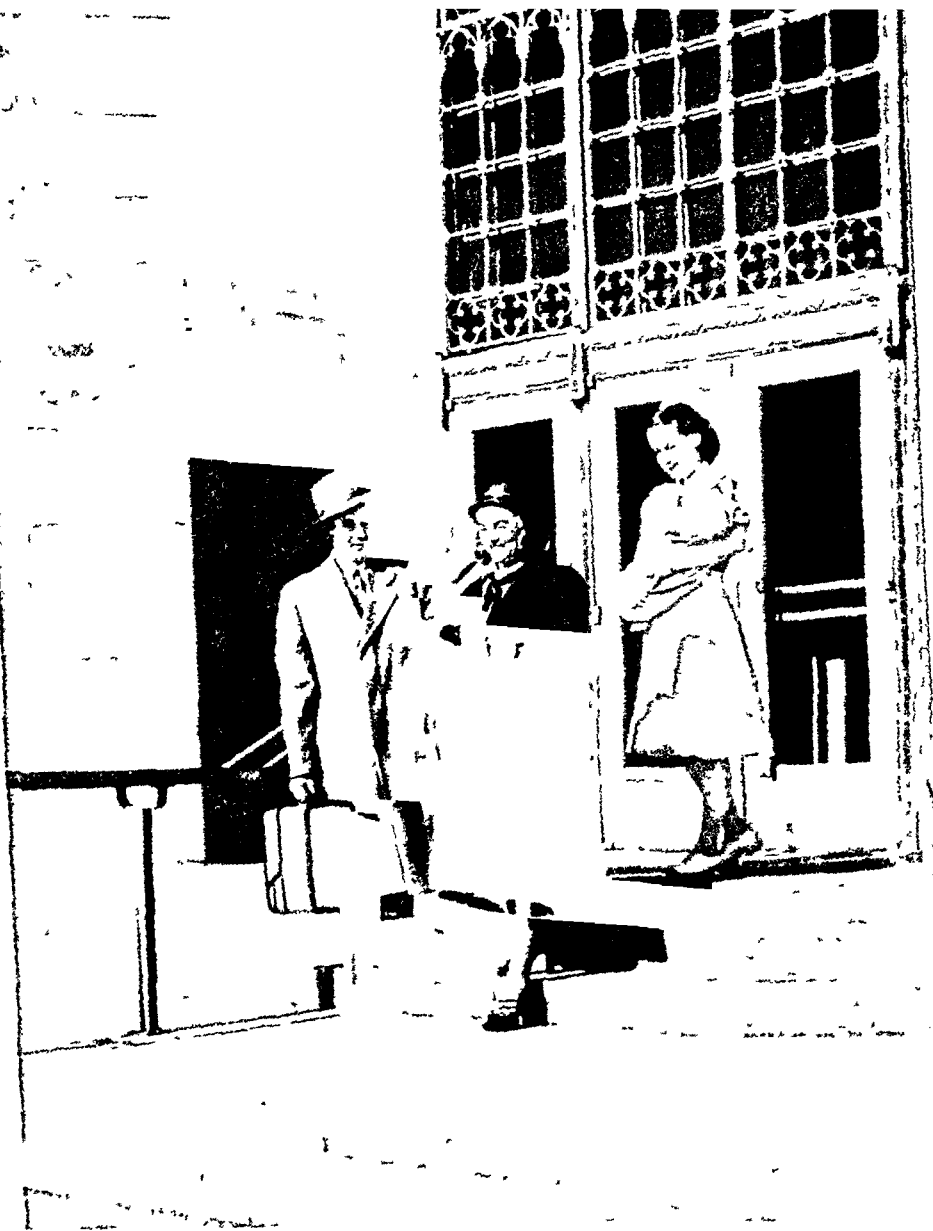
The opportunity to develop his natural aptitudes . . . to grow up with other children—like other children . . . to have full control of symptoms . . . this is Tridione's answer to a high percentage of *petit mal* victims and their anxious parents. Tridione is a synthetic anticonvulsant of low toxicity developed by Abbott Laboratories. Extensive clinical investigation has shown Tridione to be more effective than any other treatment for the symptomatic control of *petit mal*, myoclonic, and akinetic seizures. In fact, Tridione is now reported the *drug of choice* for the *petit mal* triad. Lasting benefits have been reported: in a number of cases the seizures did not return following the withdrawal of Tridione therapy. Tridione is now available for your prescription use in 0.15-Gm. Dulcet® Tablets, in 0.3-Gm. capsules and in a solution containing 0.15 Gm. per fluidrachm. For further information on the use of Tridione, write to ABBOTT LABORATORIES, North Chicago, Ill.

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1. Beckman, H., and Tatum, A. L. (1947), *The Treatment of Epilepsy*, Wis. Med. J., 46:904, September.
2. Felferman, J. L., and Weil, A. A. (1947), *Practical Aspects of Epilepsy (with special consideration of epilepsy in children)*, Med. Clin. North America, 31:1273, September.
3. Liebert, E. (1947), *Treatment of Neurological Disorders with Tridione*, Ill. Med. J., 91:311, June.
4. Lennox, W. G. (1947), *Tridione in the Treatment of Epilepsy*, J. Amer. Med. Assn., 134:138, May 10.

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"... and its administration should be started in the first two weeks after birth."¹

To initiate and maintain optimum growth . . . to prevent rickets . . . early vitamin D administration is urged. The wholly natural vitamins A and D from time-proved cod liver oil itself are provided for infant "drop dosage" in White's Cod Liver Oil Concentrate Liquid. Average antirachitic protection for infants costs about a penny a day. Liquid—Tablet—Capsule forms

¹ Margaret W. M. and Joseph P. C.
Infant Nutrition, St. Louis: The C. V. Mosby Co. 1941, p. 222

White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.



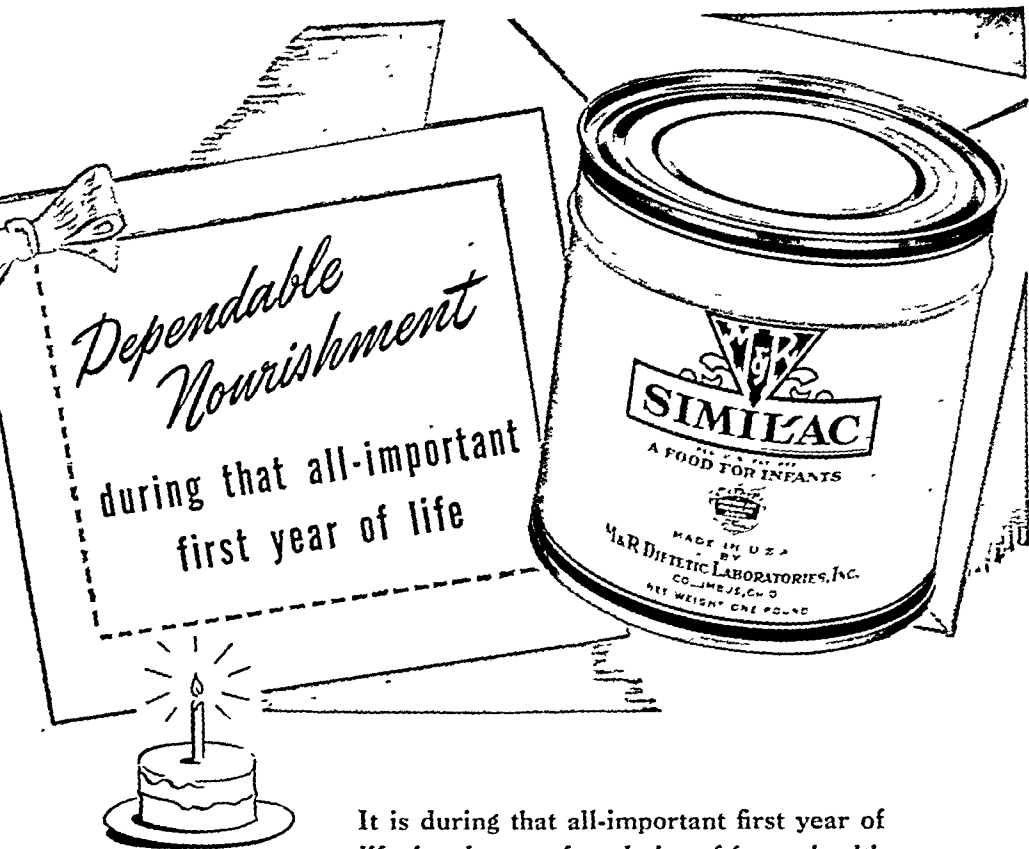
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periods
rapid
growth..."*

*"... older children require prophylactic doses of Vitamin D"¹
—it is during these periods that permanent dentition is
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¹) Kugelmass, I. N., *Newer Nutrition in Pediatric Practice*, p. 653, Lippincott, Phila., 1940.
*U.S.P. Minimum Standards

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It is during that all-important first year of life that the very foundation of *future* health and ruggedness is laid. And the well nourished baby is, in most cases, more resistant to the common ills of infancy. Similac-fed infants are notably well nourished; for Similac provides fat, protein, carbohydrate and minerals, in forms that are physically and metabolically suited to the infant's requirements. Similac dependably nourishes the bottle-fed infant—from birth until weaning.

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vitamins



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Vitamin B ₂ (Riboflavin)	75 mg
Vitamin C (Ascorbic acid)	500 U S P. units
Vitamin D (Activated ergosterol)	5 mg
Niacinamide	

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NEO-CULTOL

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Lactobacillus Acidophilus in a Refined Mineral Oil Jelly Chocolate Flavored
Dosage: One to 2 teaspoonfuls at night on retiring.
Supplied: In jars containing 6 ounces.

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as an aid in the prevention of
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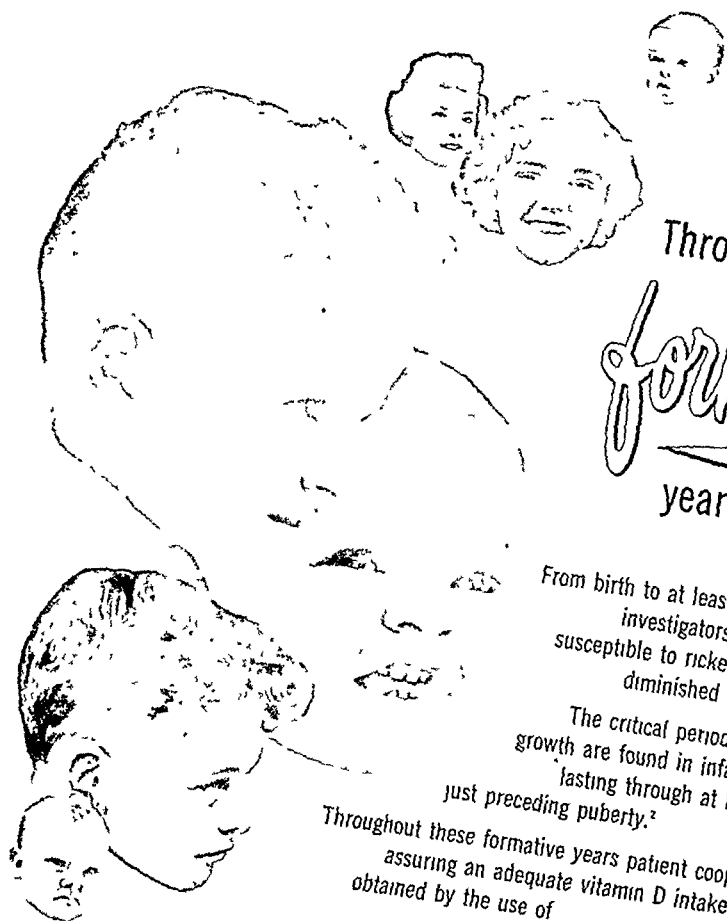
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Throughout the
formative
 years . . .

From birth to at least the age of 14 years, investigators now agree children are susceptible to rickets, with scarcely diminished frequency.¹

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 Average dose for infants 2 drops,
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¹ Follis, R H, Jackson D, Eliot M M, and Park, E A - *Am Jour Dis Child*, 66 1, July, 1943
² Stearns, G *Jour Lancet* 63-344, Nov, 1943

JUMPING-JACKS

SOFT SHOES FOR HARD WEAR



THE SHOE DESIGNED FOR YOUNG FEET

Six Months to Four Years of Age

Children's clothing needs special designing and cutting to fit young bodies. The same is true of shoes for children. It is not enough to just reduce the size of the adult style shoe and call it a child's shoe.

Jumping-Jacks have been designed to fit young feet. The unique, patented extension sole, a single piece of leather from toe to top of shoe, helps keep the heel firmly in place, and helps prevent ankles from turning.



PREVENTS FRICTION • RETAINS SHAPE

Number one (left) shows cramped foot and friction due to improper balance. Number two (right) shows foot freedom, and equal distribution of weight.



BUILDS CONFIDENCE FOR "FIRST STEPS"

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Hitherto difficult to control, impetigo has shown dramatic response to Sulfa-Ceepryn Cream—clinical reports indicating that a majority of cases are cleared *within three days*.

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Ceepryn, having a wetting action that permits quick penetration into the lesion and a bactericidal action that is particularly effective against pyogenic cocci, reinforces the action and widens the range of the sulfonamides. The special water-miscible, vanishing cream base facilitates easy spreading and

Sulfa-Ceepryn

Sulfathiazole, Sulfanilamide and Cetylpyridinium Chloride

Cream

rapid absorption of the active ingredients.

Sulfa-Ceepryn Cream is equally effective in other dermatological pyogenic infections, also adjunctively in varicose, wound, and abscess infections, following surgical drainage. Bandaging is not contraindicated. Complete literature and sample on request.

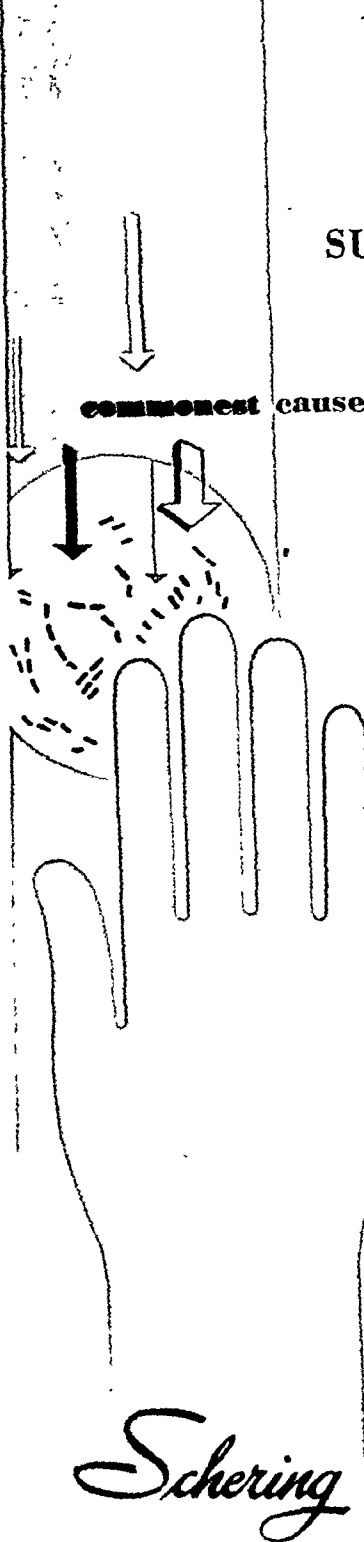
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SULAMYD* searches out and attacks *B. coli* so rapidly that "results that follow its use are uncanny. Occasionally the urine is sterile at the end of one day's treatment."¹

RECOVERY or improvement in 98% of 200 cases of acute and chronic infections of the urinary tract was noted by Welebir and Barnes,² typical of the brilliant results achieved with SULAMYD. For prophylaxis, too,

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SULAMYD (Sulfacetimide-Schering) Tablets of 0.5 Gm. in bottles of 100 and 1000. Bottles of 5.0 Gm. powder for laboratory determinations of urine and blood concentrations.

BIBLIOGRAPHY: (1) Weston, M. B.: West. J. Surg. 49:662, 1941. (2) Welebir, F., and Barnes, R. W.: J.A.M.A. 117:2132, 1941. (3) Younger, P. A.: Urol. & Gynec. Rev. 19:122, 1945. (4) Kearns, W. M., in discussion on Herrold, R. D.: Wisconsin M. J. 41:167, 1942.

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...and piling up!

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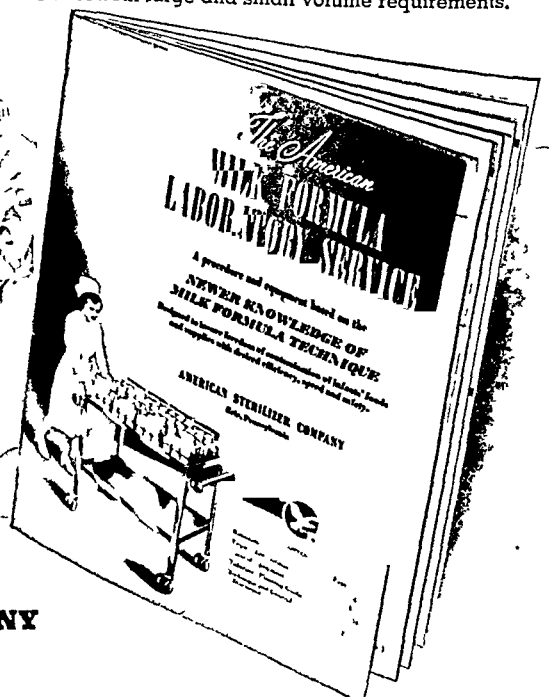
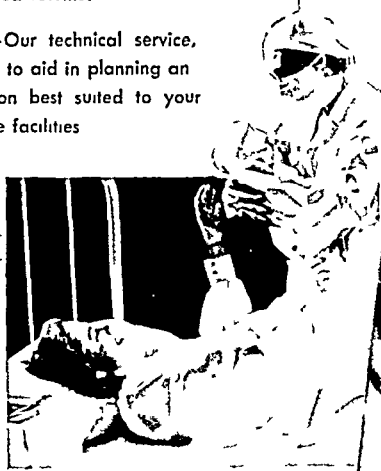
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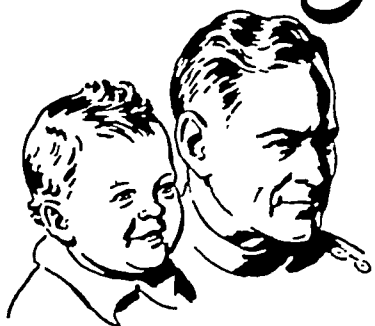


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Babies know, too, that
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is happy time.

Two people
whose judgment
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Your baby knows when he wants to
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Your baby's doctor knows what the
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There is but one more important mat-
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doctors in the selection and processing
of baby foods. They are scientifically
prepared—the natural food values
and flavor are retained in high degree.
You never go wrong with Beech-Nut.

Beech-Nut FOODS for BABIES



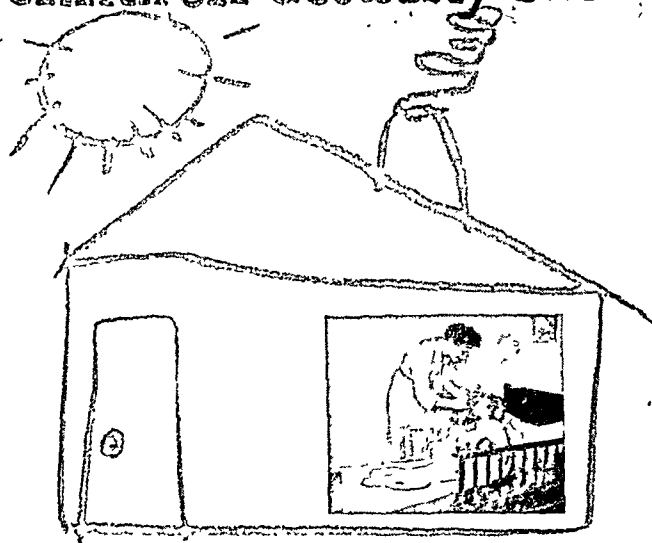
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Here's the sulfadiazine
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Exceptionally flavorful, this fluid sulfadiazine is the ideal dosage form for your young patients. They take it willingly because it tastes good. And it relieves tired parents and busy nurses of the chore of crushing tablets and coaxing a sick child to swallow an unappealing mixture.

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Eskadiazine

*Am. J. M. Sc. 210-141, 1945

*Smith, Kline
& French
Laboratories,
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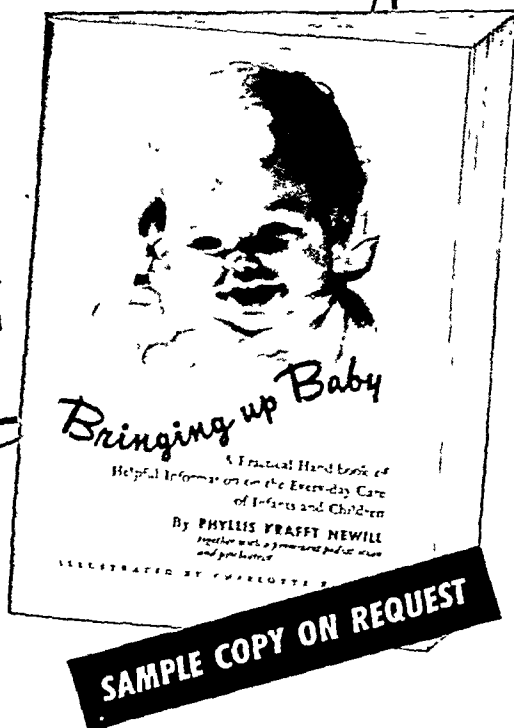
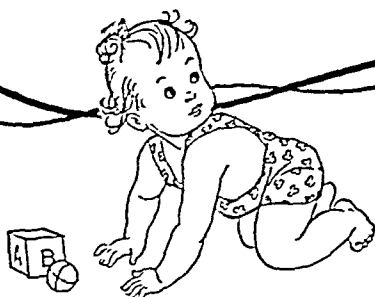
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WRITTEN BY

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Furacin Solution contains Furacin 0.2% (brand of nitrofurazone N.N.R.) dissolved in a bland, water-soluble, penetrating liquid vehicle composed of a wetting agent 0.3%, Carbowax 65% and water 34.5%.

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EACH A SPECIFIC...both effective!

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Clinically proved, the *tablet* form of Mol-Iron is conveniently suited to treating hypochromic anemias of varied etiology in older children and adults.

NOW —White's Mol-Iron is also available in *liquid* form. Particularly adapted to treating hypochromic anemias in infancy and childhood, it may be administered wherever liquid iron medication is preferred.

Potency: Each *tablet* contains 195 mg. (3 gr.) of ferrous sulfate and 3 mg. (1/20 gr.) of molybdenum oxide in the form of a stable, specially-processed complex. One teaspoonful of White's Mol-Iron *Liquid* is equivalent in its content of active ingredients to one Mol-Iron tablet.

Available: *Tablets*—bottles of 100 and 1000, *Liquid*—bottles of 12 ounces.

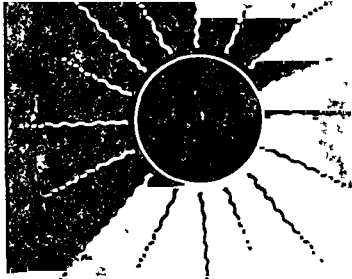
When recovery lags in hypochromic anemia because of poor iron utilization or annoying gastro-intestinal side-effects, test the demonstrable superiority of Mol-Iron. Why not prescribe this *potentiated specific* for just such a stubborn case, today?

*Healy, J. C.: Hypochromic Anemia: Treatment with Molybdenum-Iron Complex, J. Lancet 66:218 (July) 1946.

Mol-iron

Tablets
Liquid

MOLYBDENIZED FERROUS SULFATE



SCABIES

AND THE WARM SUMMER MONTHS



The seasonal increase in the incidence of scabies is effectively combated with Kwell Ointment. This unusually efficacious scabicide overcomes the infestation in most patients with a single application. No instance of dermatitis or secondary skin inflammation due to the active ingredient has been reported. Kwell Ointment presents 1 per cent of the gamma isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane in a vanishing cream base. This substance is quickly lethal for the *Sarcoptes scabiei*, but in the concentrations employed, is harmless to man. Kwell Ointment is equally valuable in the eradication of all forms of pediculosis.



Available on prescription through all
pharmacies in 2 oz. and 1 lb. jars.



C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION
17 EAST 42ND STREET NEW YORK 17 N. Y.

KWELL OINTMENT

Q: Is chewing a lost art?

A: *It needn't be . . . with Ry-Krisp.*

Ry-Krisp Stimulates Teeth and Gums.

Children need the crisp crunchiness of Ry-Krisp.
So do youngsters in the "teething age."

Ry-Krisp Satisfies Between-meal Hunger.

But does not spoil youngsters' regular mealtime appetites. Made of whole grain rye with only salt and water added, it is low in carbohydrates.

Ry-Krisp Is Good for Mealtime Nourishment.

Has the protein, minerals and B complex vitamins of whole rye.
Delicious, tempting flavor, too.

Keep Ry-Krisp in Mind for Your Young Patients.

A SERVICE FOR YOU

Allergy Diets—Wheat-free, Egg-free, Milk-free, Wheat-Egg-Milk-free and Restricted Diagnostic. Send for booklet containing single copies so you may order free diet pads as needed. Use coupon below.



RALSTON PURINA COMPANY, Nutrition Service
JP-I Checkerboard Square, St. Louis 2, Missouri

Please send, no cost or obligation: C2143 Allergy Diets Booklet.

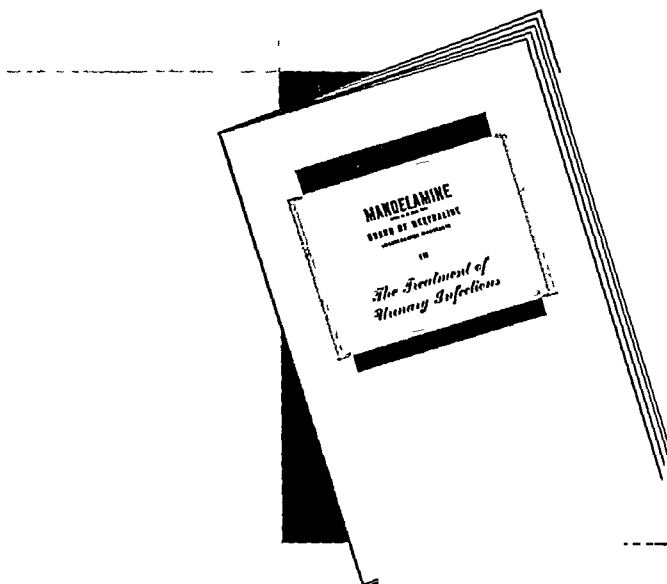
Name

Street

City

Zone State

*informative-
authoritative*



This handy, attractively illustrated booklet offers useful information on the value of MANDELAMINE,* a chemotherapeutic agent that has gained increasing preference as the urinary antiseptic of choice. It presents the results of extensive clinical and experimental studies conducted by authoritative investigators.

A copy has been mailed to you—if you have not received it, please let us know and another will be mailed promptly.



*The word MANDELAMINE is a registered trademark of Nepera Chemical Co., Inc.

Nepera Chemical Co., Inc.

MANUFACTURING CHEMISTS • NEPERA PARK, YONKERS 2, N. Y.

An Effective Adjunct in the Treatment of Certain Types of Tuberculosis

As an adjunct to conventional therapy, clinical experience has indicated that Streptomycin is the most effective chemotherapeutic agent in the treatment of certain cases of tuberculosis. In selected cases, Streptomycin has been found effective in shortening the period of disability.

The new, improved form of this valuable antibacterial agent—Streptomycin Merck (Calcium Chloride Complex)—provides three noteworthy advantages: (1) increased purity, (2) minimum pain

following injection, and (3) uniform potency.

Write for the New Booklet

"STREPTOMYCIN IN TUBERCULOSIS"

Recently published, this booklet presents abstracts of the two authoritative reports which appeared in *The Journal of the American Medical Association*, November 8, 1947, showing the results of the use of Streptomycin in more than 900 cases of tuberculosis. It will be mailed to you on request.

STREPTOMYCIN MERCK

{Calcium Chloride Complex}



FASTER MORE PROLONGED ACTION

...without over sedation

T-BARDRIN

(Angier)

Rectal Suppositories

A stable combination of ephedrine and theophylline, with adequate sedation, highly effective in a greater percentage of BOTH ASTHMA AND HAY FEVER CASES . . . especially in patients who are "epinephrine-fast".

FORMULA:

Each T-Bardrin suppository contains:
 Pentobarbital sodium 0.05 gm.
 Phenobarbital sodium 0.05 gm.

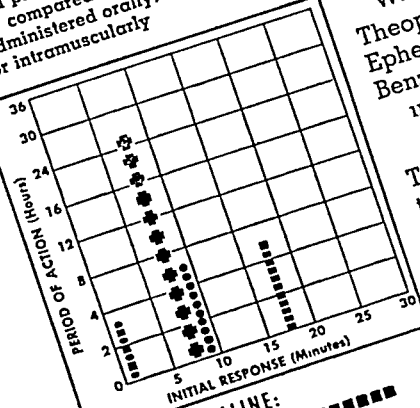
WARNING: May be habit-forming
 Theophylline 0.40 gm.
 Ephedrine hydrochloride 0.05 gm.
 Benzocaine 0.06 gm.
 in a cocoa butter base

T-Bardrin (Angier) may be employed therapeutically or prophylactically. Administration may be made at the onset of an acute attack, or routinely should the patient experience the NORMAL 24 TO 36 HOUR PERIOD OF RELIEF.

Samples and further information furnished when requested on professional letterhead

ANGIER CHEMICAL COMPANY
 Boston 34, Massachusetts

Chart illustrating initial response and prolonged action of T-BARDRIN as compared with aminophylline administered orally, intravenously or intramuscularly



AMINOPHYLLINE:

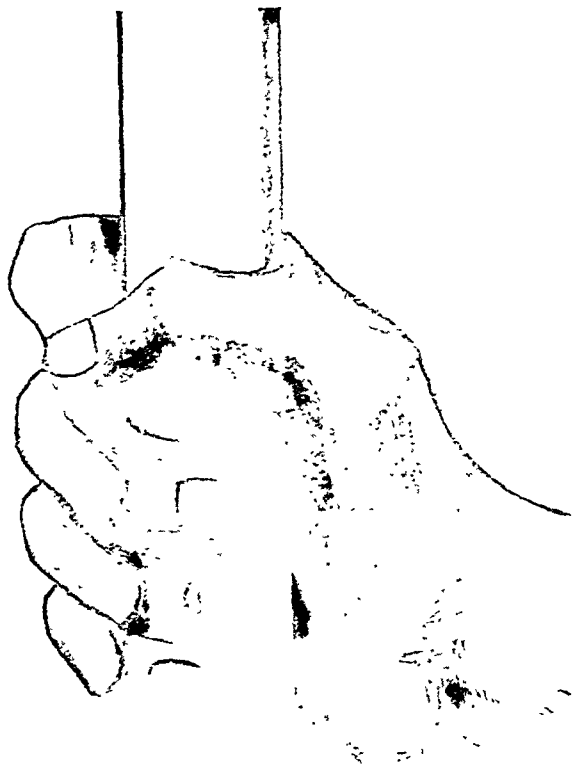
Oral

Intravenous

Intramuscular

T-BARDRIN

break the grip of an asthmatic attack



It's almost impossible to control an asthmatic attack. But you can control the symptoms with a new medicine.

First

STOP THE ATTACK

with a new medicine called **ASTHMAID**.

It's the first medicine that can stop an asthmatic attack in minutes. It's the first medicine that can stop an asthmatic attack without any side effects. It's the first medicine that can stop an asthmatic attack without any danger. It's the first medicine that can stop an asthmatic attack without any cost.

It's the first medicine that can stop an asthmatic attack without any side effects. It's the first medicine that can stop an asthmatic attack without any danger. It's the first medicine that can stop an asthmatic attack without any cost.

It's the first medicine that can stop an asthmatic attack without any side effects. It's the first medicine that can stop an asthmatic attack without any danger. It's the first medicine that can stop an asthmatic attack without any cost.

It's the first medicine that can stop an asthmatic attack without any side effects. It's the first medicine that can stop an asthmatic attack without any danger. It's the first medicine that can stop an asthmatic attack without any cost.

ASTHMAID

It's the first medicine that can stop an asthmatic attack without any side effects. It's the first medicine that can stop an asthmatic attack without any danger. It's the first medicine that can stop an asthmatic attack without any cost.



**NO DOCTOR CAN RECOMMEND
ANY BETTER EVAPORATED MILK
THAN WHITE HOUSE MILK
FOR INFANT FEEDING**

Whenever evaporated milk is prescribed for a baby's formula, no doctor can recommend any better evaporated milk than White House Milk. After repeated analysis of White House Milk's uniformity, sterility and vitamin D adequacy, we are convinced that this statement is true.

Here is why no doctor can recommend any better Evaporated Milk than White House Milk for infant feeding:

- 1 Dairy farms supplying the White House Milk Company with fluid milk must conform to high standards. In addition, all milk is rigidly tested before acceptance for use in White House Milk.
- 2 The White House Milk evaporation process results, to a high degree, in a concentrated double-rich form of the essential nutrients of fresh milk.
- 3 White House Milk equals or exceeds Government requirements for butterfat content and for total milk solids, under the present definition of the Food and Drug Administration of the Federal Security Agency.
- 4 Homogenization reduces the size of the fat globules to tiny, easily digested particles, which are uniformly dispersed throughout White House Milk.
- 5 The processing of White House Milk results in a soft, fine granular curd, which
- is almost as easily digested and assimilated in the baby's stomach as the curd of mother's milk. (White House Milk has a curd tension of zero grams—or, in other words, no tension.)
- 6 The addition of 400 U.S.P. units of pure vitamin D₃ to each pint of White House Milk aids good bone and tooth development, and optimal growth.
- 7 From the important bacteriological standpoint, White House Milk, sterilized in safe, hermetically sealed cans, satisfies the criteria of sterility.
- 8 Finally, all statements which we make about White House Milk are accepted by The American Medical Association's Council on Foods and Nutrition. And in addition, White House Milk is continually tested by The Wisconsin Alumni Research Foundation for its vitamin D content.

WHITE HOUSE MILK

There's None Better
400 U.S.P. UNITS OF
PURE VITAMIN D₃ PER PINT



Satisfaction Guaranteed by A&P—Or Your Money Back

*Not Connected With Any Other Company Using A Similar Name Or Brand.

DESITIN OINTMENT

PIONEER IN THE FIELD OF

EXTERNAL COD-LIVER OIL THERAPY

USED EFFECTIVELY IN THE TREATMENT OF Wounds, Burns, Ulcers, especially of the Leg, Intertrigo, Eczema, Tropical Ulcer, also in the Care of Infants.

Desitin Ointment contains Cod-Liver Oil, Zinc Oxide, Petrolatum, Lanum and Talcum. The Cod-Liver Oil, subjected to a special treatment which produces *stabilization* of the Vitamins A and D and of the unsaturated fatty acids, forms the active constituent of the Desitin Preparations. The first among cod-liver oil products to possess unlimited keeping qualities, Desitin, in its various combinations, has rapidly gained prominence in all parts of the globe.

Desitin Ointment is absolutely non-irritant; it acts as an anti-phlogistic, allays pain and itching; it stimulates granulation, favors epithelialisation and smooth cicatrisation. Under a Desitin dressing, necrotic tissue is quickly cast off; the dressing does not adhere to the wound and may therefore be changed without causing pain and without interfering with granulations already formed; it is not liquefied by the heat of the body nor in any way decomposed by wound secretions urine, exudation or excrements

DESITIN POWDER

Indications: Minor Burns, Exanthema, Dermatitis, Care of Infants, Care of the Feet, Massage and Sport purposes.

Desitin Powder is saturated with cod-liver oil and does not therefore deprive the skin of its natural fat as dusting powders commonly do. Desitin Powder contains Cod Liver Oil, (with the maximum amounts of Vitamins and unsaturated fatty acids) Zinc Oxide and Talcum

Professional literature and samples for Physicians' trial will be gladly sent upon request.



Sole Manufacturer and Distributor in U.S.A.

DESITIN CHEMICAL COMPANY

70 SHIP STREET • PROVIDENCE • RHODE ISLAND

Formulac

**a flexible
formula basis**



FORMULAC Infant Food is a product of National Dairy research — a concentrated milk containing all the vitamins and minerals a normal infant is known to need. The vitamins are in the milk itself, reducing the risk of error or oversight in supplementary administration.

The only carbohydrate in **FORMULAC** is the normal lactose found in cow's milk. This permits you to prescribe both the type and amount of carbohydrate each individual child requires.

FORMULAC is in convenient liquid form, for easy preparation. The addition of water and sugar, at your discretion, creates a complete infant diet for normal and difficult feeding cases.

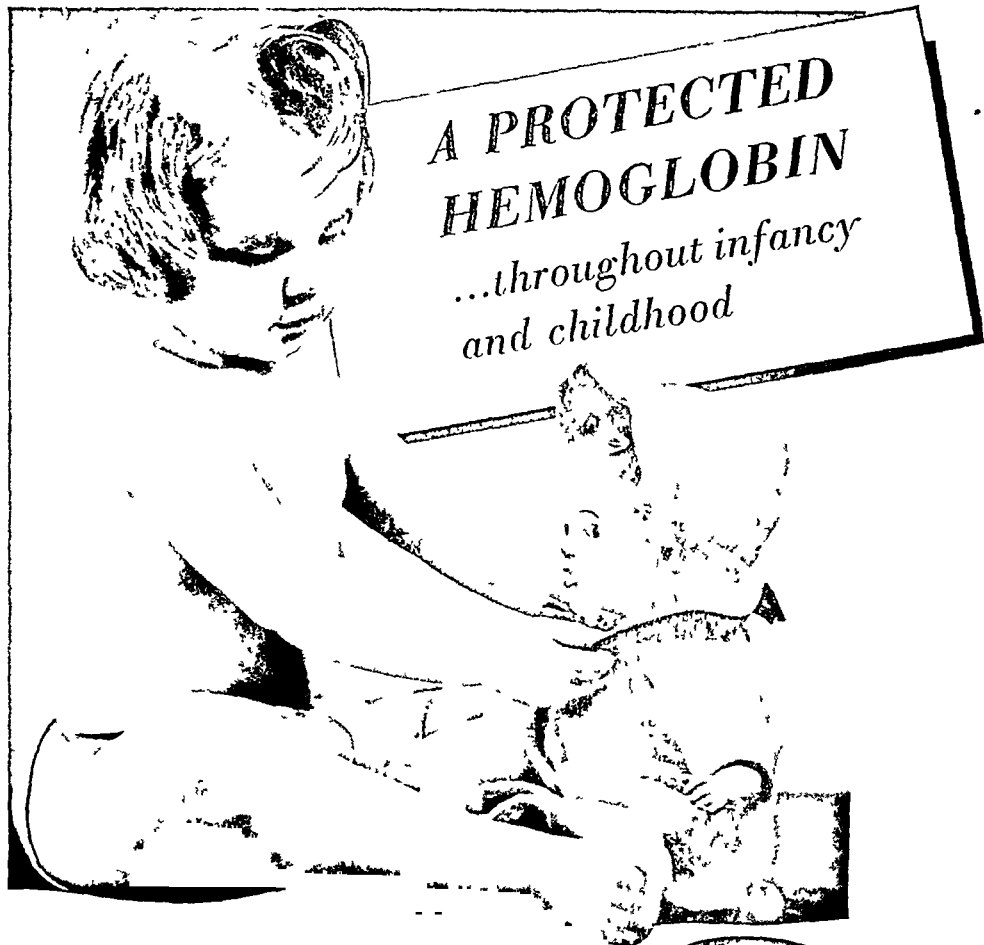
FORMULAC is promoted ethically. It has been clinically tested and proved, and retains its vitamin potency on storage. Economically priced, this product of National Dairy research is available at drug and grocery stores everywhere.

DISTRIBUTED BY KRAFT FOODS COMPANY

NATIONAL DAIRY PRODUCTS COMPANY, INC.
NEW YORK, N. Y.

For further information about **FORMULAC**, drop a card to National Dairy Products Co., Inc., 230 Park Avenue, New York 17, N. Y.





A PROTECTED HEMOGLOBIN

...throughout infancy
and childhood

During the early years of life the expanding blood volume makes heavy demands upon iron stores to satisfy hemoglobin requirements.

Copperin "B" promptly replenishes these inroads upon iron reserves—protecting the hemoglobin levels. Due to the presence of the catalyzing copper sulphate *all* of the iron ammonium citrate is available for use. Hence, the iron is present in very small quantity—32 Mg. per capsule. Copperin is well tolerated, causes no stomach irritation and being water soluble, may be taken in fruit juices, milk or feeding formula.

Write for samples and pediatrician's literature

MYRON L. WALKER CO. INC.

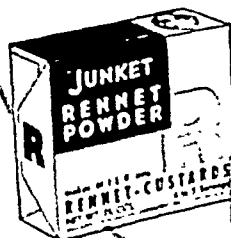
Mount Vernon, New York



GIVING MILK THE GREEN LIGHT!



"JUNKET" is the trade-mark of Chr. Hansen's Laboratory, Inc., for its rennet and other food products, and is registered in the United States and Canada.



WHEN MILK IS A VITAL PART of the daily regimen, such as in infancy, childhood, pregnancy, and for gastro-intestinal, postoperative and geriatric conditions—a serious aggravation of the dietary problem may occur for those patients who (either for physiologic or psychologic reasons) are unable to ingest this essential nutrient.

In such cases, the *red light* of milk refusal may be quickly changed to the *green light* of eager acceptance—by transforming the liquid milk into deliciously flavored, tasty rennet desserts, through the medium of rennet powder or household rennet tablets.

Young and old alike relish these temptingly smooth custard-like desserts which incorporate the uncooked milk—with all nutritional factors unchanged—into a variety of delicious, colorful rennet desserts. They're so simple to prepare—and are more easily digested than milk itself, because of the softer, more friable curds formed in the stomach.

"JUNKET" RENNET POWDER—already sweetened—comes in six popular flavors;

"JUNKET" RENNET TABLETS are not sweetened or flavored—just add sugar and flavor to taste.

Delicious, highly acceptable rennet desserts may be made with either.

"JUNKET" BRAND FOODS

Division of Chr. Hansen's Laboratory, Inc.
LITTLE FALLS, N. Y.

B-25

the preferred

PERTUSSIS IMMUNE SERUM—*human* IN VACUUM-DRIED FORM



This serum—established as the agent of choice in the treatment of, and passive immunization against, whooping cough—is now available to physicians everywhere.

Vacuum dehydration by the 'LYOPHILE' process provides high stability (a 5-year dating) and permits optimal concentration.

Standard price: \$6.50 per dose.

i.e., vial containing 20 cc. of serum, vacuum-dried.

3 to 4 doses generally required in treatment.

24-hour service to handle telegraphic orders.

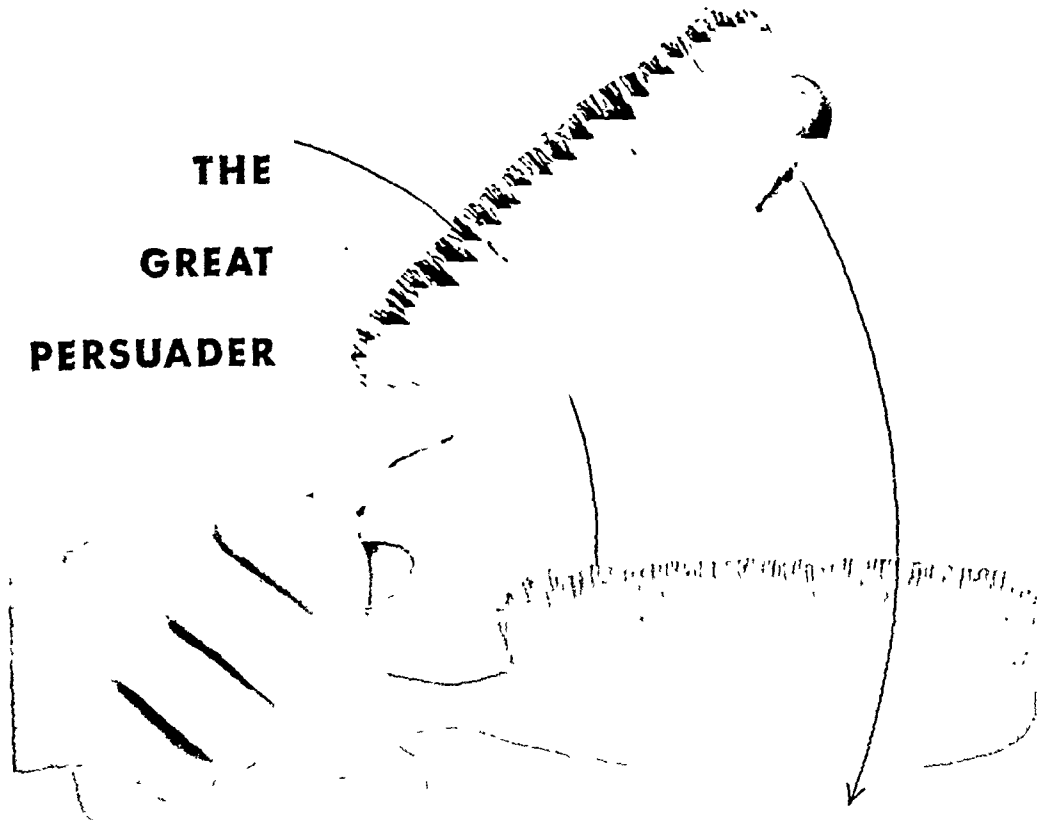
For literature and full information, write to:

The **PHILADELPHIA
SERUM**

EXCHANGE *A Non-profit Organization*

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
1740 Bainbridge Street, Philadelphia 46, Pennsylvania

THE GREAT PERSUADER



All too often irate parents resort to a "good licking" for children who refuse to eat. The therapeutic merits of such a procedure are of course not medically recognized, since anorexia often is more than a stubborn personality defect.

More effective than punishment is the stimulation of B complex on appetite. 'Ryzamin-B' No. 2 has proved especially effective because of a pleasant taste-appeal which children relish. Containing the *natural* B complex as a concentrate of *Oryza sativa* (American rice) polishings, 'Ryzamin-B' No. 2 is also potently fortified with synthetic B factors. Children enjoy its rich, honey-like flavor any way it is given—right from its special measuring spoon, as a delicious spread with jam or peanut butter, or dissolved in milk, fruit juice and other beverages.

'RYZAMIN-B' BRAND B-VITAMIN CONCENTRATE NO. 2

WITH 100% B-VITAMIN, INCLUDING VITAMINS B1, B2, B3, B6, B12, AND PANTOTHENIC ACID, IN A TASTELESS, SWEET, AND NON-TOXIC FORM.

MADE IN U.S.A. - PATENTED

WILLIAMS' PINK PILLS & POWDERS CO., INC., 100 EAST 41ST STREET, NEW YORK 17

This Metabolic Burden Should be Avoided

That persons who eat an inadequate breakfast or skip breakfast entirely find difficulty in obtaining their needed nutrients from the other two meals of the day is becoming increasingly apparent. A nutritionally unsound breakfast thus imposes an unnecessary burden not only on the other two meals, but also upon the organism.

For this reason, nutritionists are unanimous that breakfast should provide from one-fourth to one-third of the day's caloric and nutrient needs. In planning a nutritionally sound breakfast, a widely endorsed basic breakfast pattern serves well as the nucleus around which the morning meal can be built. Providing fruit, cereal, milk, bread and butter, this pattern supplies virtually all essential nutrients in balanced proportion. It is economical and readily available in all communities. The cereal serving, consisting of hot or ready-to-eat breakfast cereal, milk, and sugar, is an important main dish of this meal. It adds significant amounts of essential nutrients and makes possible wide variety because of the many kinds of cereals available.

The table indicates the nutrient values of this basic breakfast and the contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk and 1 teaspoonful of sugar.



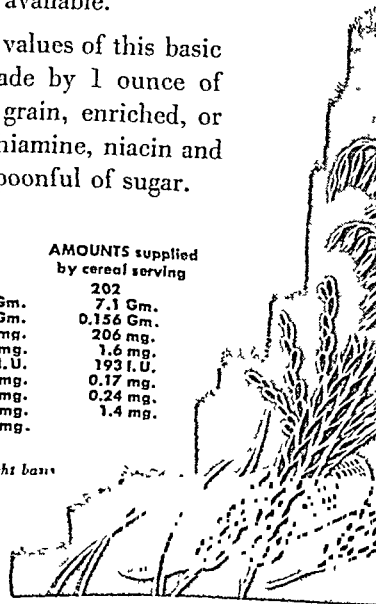
The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

BASIC BREAKFAST	TOTALS supplied by Basic Breakfast	AMOUNTS supplied by cereal serving
Orange juice, 4 oz ;	CALORIES..... 611	202
Ready-to-eat or	PROTEIN..... 20.7 Gm.	7.1 Gm.
Hot Cereal, 1 oz ;	CALCIUM..... 0.465 Gm.	0.156 Gm.
Whole Milk, 4 oz ;	PHOSPHORUS . 488 mg.	206 mg.
Sugar, 1 teaspoon,	IRON..... 3 mg.	1.6 mg.
Toast (enriched,	VITAMIN A..... 1074 I.U.	193 I.U.
white), 2 slices;	THIAMINE..... 0.52 mg.	0.17 mg.
Butter, 5 Gm.	RIBOFLAVIN..... 0.57 mg.	0.24 mg.
(about 1 teaspoon);	NIACIN..... 2.3 mg.	1.4 mg.
Whole Milk, 8 oz.	ASCORBIC ACID.. 64.8 mg.	

*Composite average of all breakfast cereals on dry weight basis

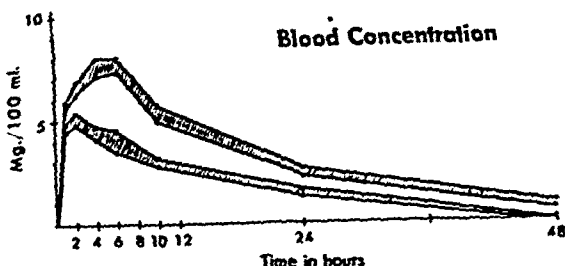
CEREAL INSTITUTE, INC.

A research and educational endeavor devoted to the betterment of national nutrition
135 South La Salle Street • Chicago 3

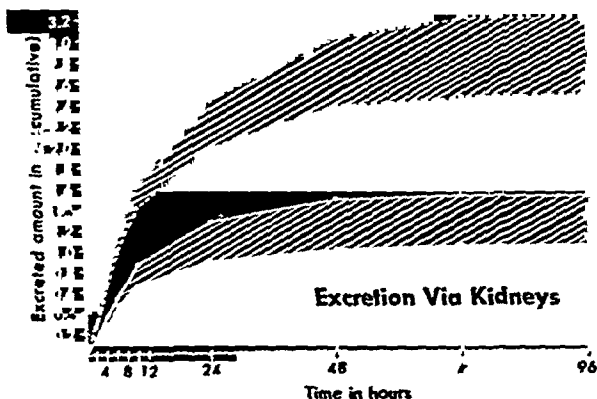


BALANCED SAFETY

Designed upon
Sound Physical
Principles



Graphs following single oral doses of 2 grams and 4 grams of "Sulfa-Combination" of
Sulfadiazine 37%
Sulfathiazole 37%
Sulfamerazine 26%



GLUCOSulfas

NEW BALANCED BUFFERED TRIPLE MIXTURE

GLUCOSulfas, for the first time, provides a balanced clinically-tested combination of three sulfonamides based upon the excretion rate of each component,¹ and buffered with purified sodium lactate. Thus, GLUCOSulfas even in high dosage, appears to eliminate the risk of concret formation, with enhanced bacteriostatic effectiveness. It is an unflavored, smooth, free-flowing product with the unvarying stability that assures uniform dosage from the first to the last measured cc. from a container.

Composition: Each teaspoonful (5 cc.) of GLUCOSulfas contains 0.5 gram of balanced sulfonamides in the following proportions—Sulfadiazine 37%, Sulfathiazole 37%, Sulfamerazine 26% in a purified sodium lactate-glucose base. Sulfamerazine, due to a slow rate of excretion, gives rise to concretions in a lower dose than sulfadiazine or sulfathiazole, and is, therefore used in smaller proportions. Supplied: Pint bottles.

¹ Frost, A. P., et al. *Exp. Med.* 11: 7-10, 1947.

DONLEY-EVANS  & COMPANY • ST. LOUIS 15, MISSOURI



*"—that Kaomagma certainly
did the trick"*



6 and 12 fl. oz.

One of the gratifying things about prescribing Kaomagma is the knowledge that your patients will get *quick* symptomatic relief from diarrhea . . . comfort, a feeling of security.

Kaomagma rapidly controls diarrhea. Kaolin colloiddally dispersed in alumina gel adsorbs irritants, consolidates fluid stools, soothes and protects the irritated mucosa.

Dosage is self-limiting—2 tablespoonfuls in water at first, then 1 tablespoonful after each movement until normal.

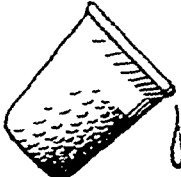
KAOMAGMA®

Kaolin in Alumina Gel

WYETH INCORPORATED • Philadelphia 3, Pa.



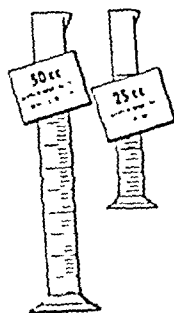
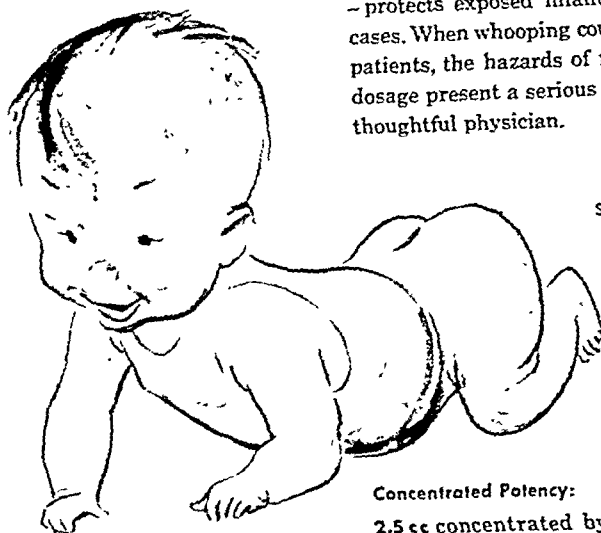
00

A thimbleful of  dosage...

for a handful of baby . . . **2.5cc HYPERTUSSIS**

concentrated human anti-pertussis globulin
- protects exposed infants - treats critical cases. When whooping cough attacks small patients, the hazards of massive repeated dosage present a serious problem to every thoughtful physician.

2.5 cc Hypertussis provides the specific solution for therapy or passive prevention. The advantages are evident:



2.5cc HYPERTUSSIS

highly concentrated and purified gamma globulin of pooled human serum from healthy donors hyperimmunized with Super-Concentrate Phase 1 Pertussis Vaccine

The Specific Cutter Blood Fraction for Whooping Cough...

Concentrated Potency:

- 2.5 cc concentrated by fractionation to contain the antibody equivalent of 25 cc hyperimmune human serum.
- 2.5 cc delivers consistent gamma globulin potency in constant measured doses.

Small Volume Dosage:

- 2.5 cc concentrated gamma globulin reduces dosage volume 75% - minimizes injection trauma - permits repetition when required.

Homologous, sensitivity-free:

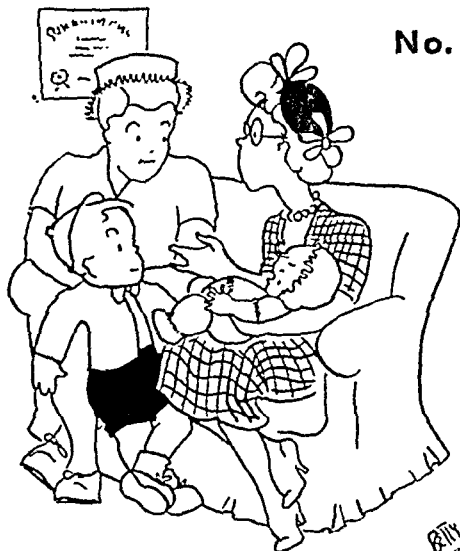
- 2.5 cc clear liquid homologous protein, Hypertussis is ready for intramuscular injection - avoids danger of reactions and serum sensitivity.

For 10-fold concentration in small volume dosage
- specify **CUTTER 2.5cc HYPERTUSSIS**
Anti-Pertussis Serum (Human)

CUTTER LABORATORIES • BERKELEY, CALIFORNIA

The Doctors' Album of New Mothers

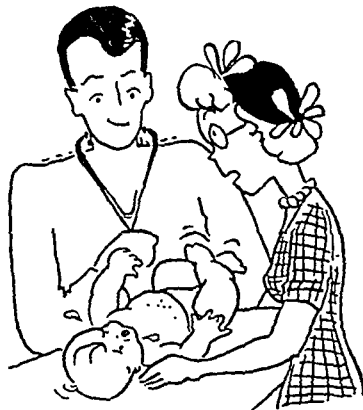
No. 22: HELPFUL MRS. HAYDEN



Mrs. Hayden has melting blue eyes, yellow hair, little flowery hats, and a will of high-grade surgical steel. She often thinks (and out loud, too) that she would have made a wonderful diagnostician.

BY
FRANK
BLUNT

"Doctor," she declares (as you sigh resignedly), "little Janie has an advanced case of *morbilli rubeola*. I knew it the minute I looked at her poor tummy just now. It's speckled like a trout!"



Mrs. Hayden and also mothers who are *not* medical geniuses often mistake common externally caused infant skin irritations for something more serious.

Many doctors ward off such unnecessary alarms by recommending the regular use of Johnson's Baby Powder to help prevent prickly heat and similar infant discomforts.

Smooth, gentle Johnson's Baby Powder is the choice of more doctors and nurses than all other brands put together.



JOHNSON'S BABY POWDER

Johnson & Johnson





wherever

s o a p causes

aggravates, or prolongs

**DIAPER RASH and
INFANTILE ECZEMAS**

LOWILA

CAKE for skin cleansing

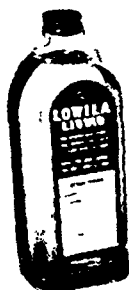
The only detergent cake which is entirely soapless yet cleanses as well as soap. No alkali whatsoever, pH approximates normal skin, never irritates. Less slippery than ordinary soap so mother can hold baby more firmly while bathing. Good lather.

**completely
SOAPLESS**

**non-irritant
lathering
detergents**

LIQUID for clothes and household

Washes diapers, bed clothes, infant wear beautifully; soapless and non-irritant in proper dilution. Does not leave the alkaline, irritating residue left by soaps.



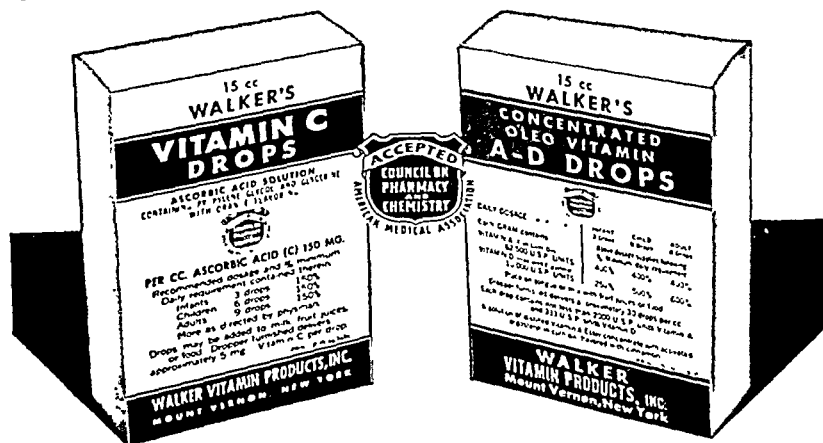
For SAMPLES and literature **SEND COUPON**
WESTWOOD Pharmacal Corp.
468 Dewitt St., Buffalo 13, N. Y., Dept. J.P.
Convince me with **TRIAL SUPPLY** and literature
LowILA cake and liquid

Dr.....

Address.....

WALKER

COUNCIL-ACCEPTED VITAMIN DROPS



Potent, convenient, flexible dosage form
Designated for use in pediatrics and geriatrics

VITAMIN C DROPS

Each drop supplies 5 mg. of vitamin C

Supplied in dropper bottles of 15 cc.

CONCENTRATED OLEO VITAMIN A-D DROPS

Each drop supplies 2,000 units vitamin A, 333 units vitamin D

Supplied in dropper bottles of 15 cc. and 60 cc.

Walker

VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.

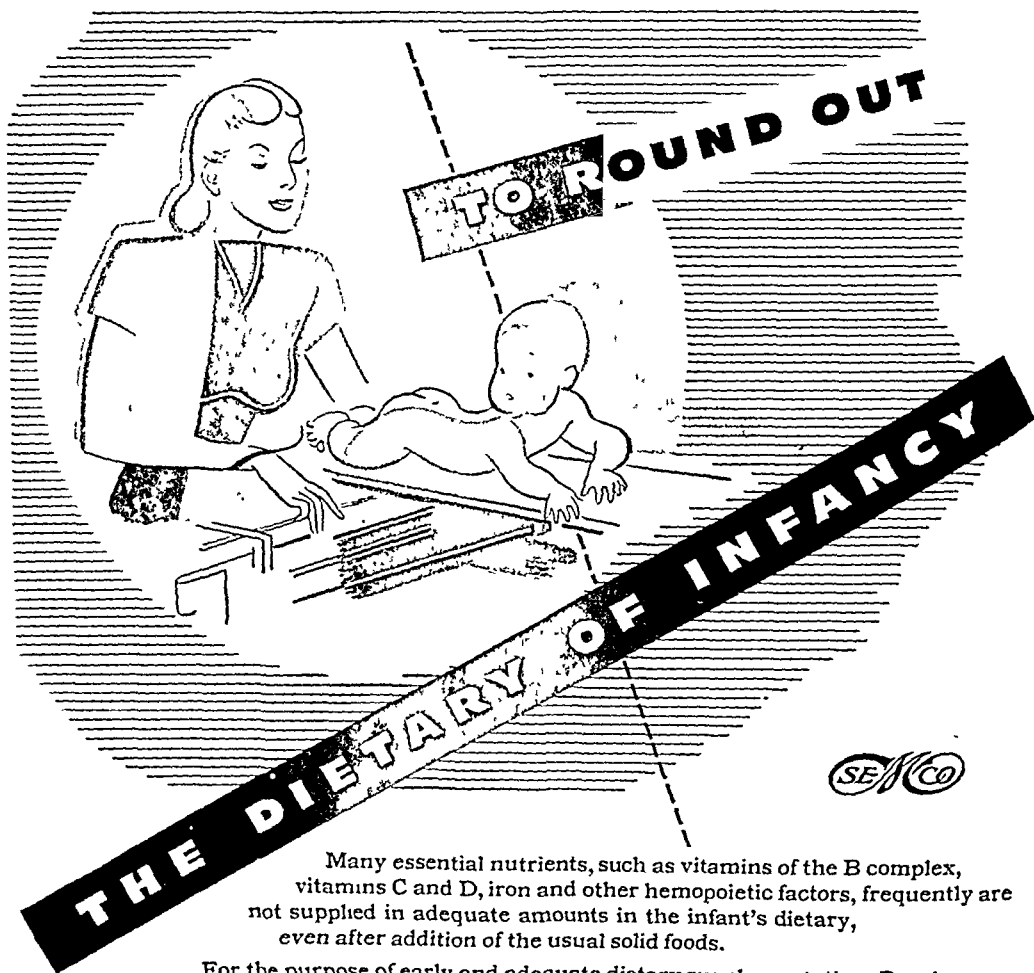


Baby Breck

O I N T M E N T For Aiding Diaper Rash

Baby Breck Ointment helps to prevent and eliminate diaper rash. A bland ointment with a minimum allergic reaction is often necessary at diaper changes to protect the extra sensitive skin of babies. Baby Breck Ointment contains lanolin and may be used on other chafed areas of the skin.

JOHN H. BRECK, INC. MANUFACTURING CHEMISTS SPRINGFIELD 3 • MASSACHUSETTS
CANADIAN ADDRESS • 116 SLATER STREET • OTTAWA



Many essential nutrients, such as vitamins of the B complex, vitamins C and D, iron and other hemopoietic factors, frequently are not supplied in adequate amounts in the infant's dietary, even after addition of the usual solid foods.

For the purpose of early and adequate dietary supplementation, Droplex proves a convenient means of supplying these nutritional essentials.

Each cc. (15 minims) provides:

Thiamine Hydrochloride (B ₁)	4.0 mg	Liver Concentrate 1-20	400.0 mg.
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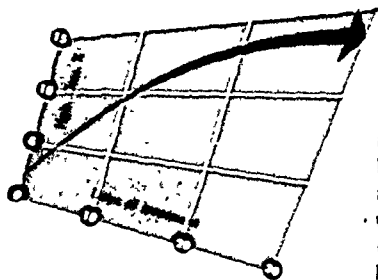
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2. Reznikoff, P., and Gorbil, W.P.: *Jour. Clin. Investigation*, 16:517, July, 1937. 3. Teeter, E.J.: *J.A.M.A.*, 127:973, April 14 1945.

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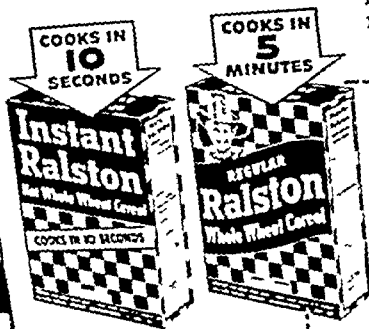
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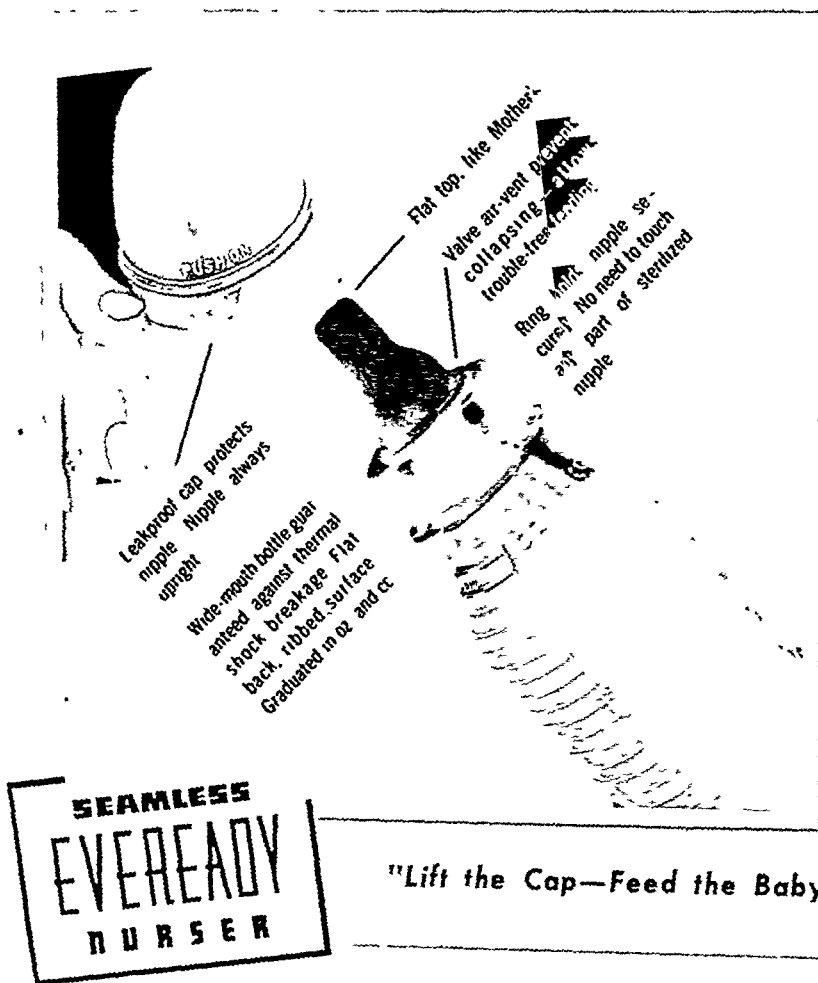
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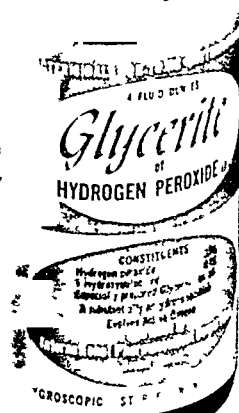
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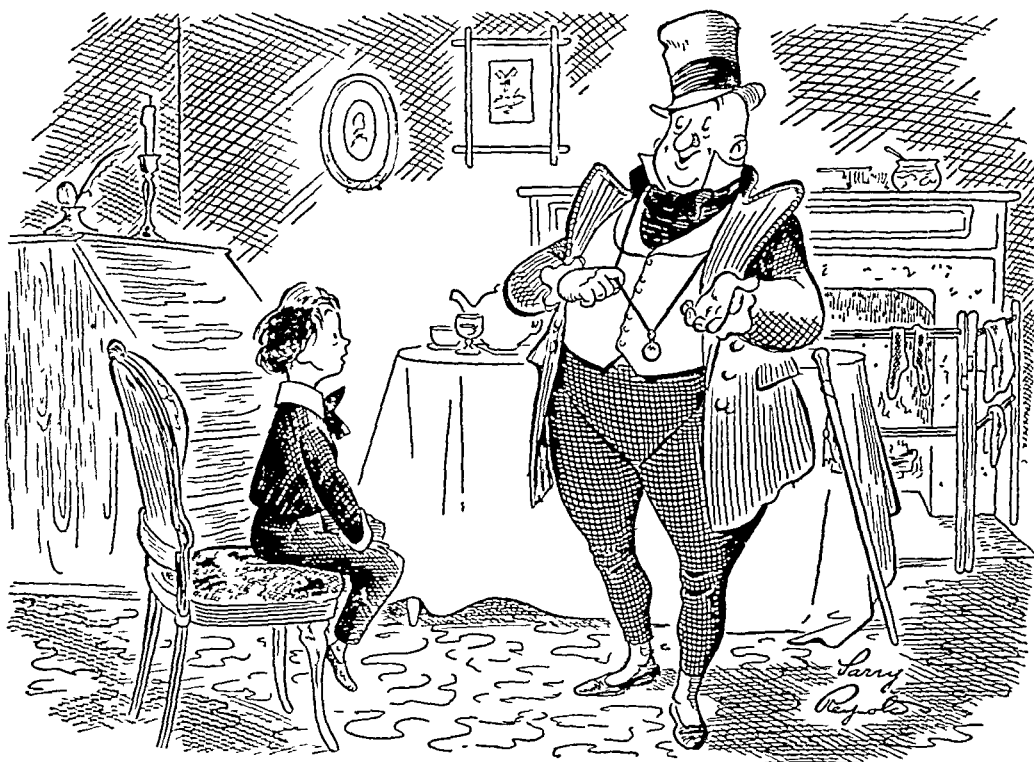
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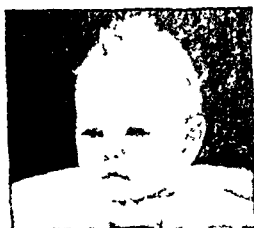
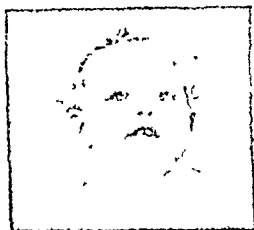
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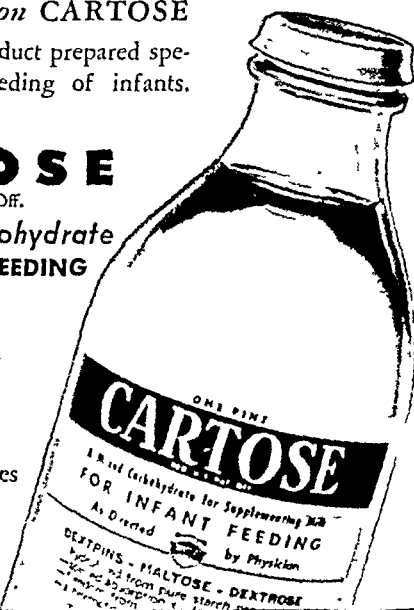
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The Journal of Pediatrics

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Original Communications

A REVIEW OF BOECK'S SARCOID WITH ANALYSIS OF TWELVE CASES OCCURRING IN CHILDREN

ROSS B. CONE, M.D.
DURHAM, N. C.

BOECK'S sarcoid* is a specific chronic infectious disease of unknown etiology, producing characteristic lesions distinguishable from other infectious granulomas such as tuberculosis and syphilis. It occurs more frequently in females and is essentially a disease of adult life. It appears more commonly among rural folk living in north temperate zones (Scandinavia, northern Europe, England, and North America). In the United States, sarcoidosis is seen with some prevalence in the North Carolina area, particularly in young adults but also in children. The Negroid¹⁰ and darker skinned races are more frequently affected with this condition, but it may occur in all races.

Typically, sarcoidosis runs a chronic relapsing course producing comparatively mild constitutional symptoms. Practically any organ or tissue in the body may be involved. However, the more common manifestations occur in the skin, lymph nodes, eyes, salivary glands, lungs, and bones of the hands and feet especially.

Because groups of organs may be involved in a variety of combinations, a great number of clinical syndromes result. This has led to the adoption of terms describing such clinical entities as uveoparotid fever. In general, it may be said that all extracutaneous lesions are characterized by their latency and tendency to spontaneous regression in contrast to the much more chronic behavior of the skin lesions.

THEORIES OF ETIOLOGY

Three of the more prevalent schools of thought concerning the etiology of this disease are as follows:

1. An anergic form of tuberculosis.
2. A *Mycobacterium* somewhere between the tuberculosis and leprosy organisms; a pleomorphic variant.¹⁹
3. An as yet undiscovered virus.

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital, Durham, N. C.

*This disease is also found in the literature under the terms "sarcoidosis," "benign lymphogranulomatosis," "Mortimer's malady," "Besnier-Schaumann-Boeck's disease," "Hutchinson-Boeck's disease," "lupus pernio," "uveoparotid fever," and a few other less well-known names.

In support of the first and largest school is the microscopic picture which strongly resembles that of tuberculosis. It is the so-called hard tubercle, composed of granulomatous, large, pale, polygonal epithelioid cells collected in isolated nests or well-defined nodules. Occasional multinucleated, pale Langhans' giant cells complete the picture. There is a striking scarcity or even absence of lymphocytic tissue response. Central necrosis and caseation are almost never found. Months pass without significant histologic change.

A few cases have been cited³ in which acid-fast organisms were demonstrated in skin lesions and nasal mucous scrapings. Two Japanese workers⁷ have even reported culturing the tubercle bacillus from skin lesions. Generally speaking, however, acid-fast bacilli can rarely if ever be found in lesions of skin or lymph nodes, and animal injections have proved fruitless. Koch's postulates have not been fulfilled.^{5, 16} In addition, the skin test reaction to old tuberculin has been conspicuously feeble or negative. Those who uphold the view that the disease is caused by the tubercle bacillus,^{1, 2, 3} explain the lack of skin sensitivity on Jadassohn's theory of anergy. There are, however, cases on record in which there have subsequently developed positive tuberculins after proved pulmonary tuberculosis developed. It has also been observed, curiously enough, that the lesions of sarcoidosis disappear upon development of active tuberculosis.

In some cases of sarcoidosis, bone changes in hands and feet, trophic changes of the nails, and skin lesions have closely resembled leprosy,²⁰ giving rise to the theory that there is an acid-fast organism at the base of this disease which has some of the characteristics of the tubercle bacillus and some of the characteristics of the leprosy bacillus. Perhaps some by-products of an acid-fast organism are responsible for the symptoms.

Supporting a virus etiology for this disease is the definite tendency toward neutropenia and leucopenia, and the fact that no clearly demonstrable etiological organism has yet been found.

SYMPTOMATOLOGY

Sarcoidosis is usually insidious in onset, the earliest manifestations being skin lesions in about 50 per cent of cases and/or lymphadenopathy. There is seldom more than slight constitutional reaction in the early stages, with temperature rarely exceeding 100° F. even with major degrees of pulmonary involvement. Typical complaints are of mild malaise, slight fever, vague abdominal distress, nausea, vomiting, diarrhea, pain in chest, nonproductive cough, weakness, weight loss, pain in eyes, photophobia, dimming of vision, night sweats, and arthralgia.

Longcope emphasizes that symptoms are caused by "mechanical interference with the function of the organs rather than by any form of intoxication."⁶ Sarcoid lesions by mechanical pressure on normal tissue displace or destroy it.

SKIN LESIONS

Boeck found it convenient to divide skin sarcoidosis into three types of eruptions.

1. Small, firm, elastic round or oval papules (1 to 5 mm.) having a brown, bluish, red, or violaceous color, with no surrounding erythema, induration, or anesthesia. These papules are most frequently seen on the face, back of shoulders and neck, extensor aspects of the arms, and particularly around the eyelids and nose.

2. Similar but larger nodules.

3. Skin may be diffusely infiltrated with thickened plaques (lupus pernio) over nose, face, and ears. The tense skin over the affected areas may be blue with tiny yellow granules at the margins.

These lesions are often dry and may have small scales or crusts on them but seldom itch or break down. Occurrence along the margin of the eyelids should be especially emphasized, for it is infrequent in other diseases involving the skin.¹² Lesions on the palms and soles are rare but may occur. As the nodules age they become darker and may finally leave only an atrophic pigmented scar.^{5, 14}

LYMPHADENOPATHY

Submental, pre- and postauricular, posterior cervical, occipital, and epitrochlear nodes are most frequently found to be enlarged. However, any other lymphoid tissue in the body may be involved. The nodes range in size from 4 to 6 mm. and are firm, rubbery, discrete, and usually painless. Harrell⁵ states that "enlargement of nodes along the borders of the muscles of the shoulder girdle or along the course of the major lymphatic vessels of the arm is rarely observed in other conditions" and therefore may be of significant diagnostic aid.

EYE INVOLVEMENT

Invasion of the eye often results in keratitis and iridocyclitis (uveitis). However, involvement of any or all of the structures of the eye is comparatively common during some stage of the disease. Under the slit lamp one can frequently see yellowish white, irregularly shaped opacities of the cornea, which, in time, resolve into numerous discrete, "mutton-fat," amorphous deposits on Descemet's membrane. Other common complications are conjunctivitis, aqueous turbidity, vitreous hemorrhage, optic neuritis, neuroretinitis, chorioretinitis, glaucoma, and cataract.

Of the thirty-one patients in Longcope's "Hopkins series" eye involvement occurred in sixteen cases and was the first manifestation of this disease in twelve of the sixteen cases. In some instances, lesions of the cornea, iris, or uveal tract may heal, leaving scars and synechias, but too often sight is destroyed or enucleation required.

UVEOPAROTID SYNDROME

In this syndrome the previously mentioned eye involvement is often preceded by nonspecific symptoms of lassitude, malaise, and indefinite gastrointestinal complaints. Intermittent fever may occur, the temperature usually not exceeding 102° F. Then there develops a firm, painless swelling of the parotid glands, which may not arise simultaneously but is usually eventually bilateral. The patient may experience dryness of the mouth, but mastication is seldom embarrassed by parotid swelling. Induration of the glands may be permanent.

A third component develops in the majority of patients with the onset of seventh-nerve paralysis, unilateral or bilateral, a few days to a few months after the onset of parotitis. Lower facial distribution is more involved than upper. Ordinarily, facial nerve palsy subsides along with the parotitis.

PULMONARY SYMPTOMS

Aside from a dry, hacking cough and/or dyspnea there are seldom any symptoms referable to the chest. The patient may complain of pain in the axilla or beneath the scapula. Occasionally he will complain of a low-grade intermittent fever. On physical examination one may elicit interscapular dullness, bronchial breath sounds, râles, and sometimes friction rubs. Patients with extensive lung involvement appear to be more susceptible to secondary lung infections and may go on to develop bronchopneumonia or tuberculosis.

CARDIAC INVOLVEMENT

Patients with Boeck's sarcoid have been known to develop involvement of the heart and its surrounding structures. There may be cardiac enlargement, arrhythmias, electrocardiographic changes, or any of the symptoms of various degrees of myocardial failure.⁸ More than nine cases have been reported in the literature in which, at autopsy, sarcoids were revealed in the myocardium and/or pericardium. Of a series of thirty-one cases of sarcoid at Johns Hopkins,³ six patients presented evidence during life of some derangement of the heart's action. Three died, and autopsies performed on two showed sarcoidosis of the myocardium and pericardium.

CENTRAL NERVOUS SYSTEM LESIONS

Neurological symptoms are for the most part rare, but cases have been reported with paralysis of the soft palate, dysphagia, intercostal neuralgia, paralysis of the vocal cords, deafness, ptosis, wasting of the hand muscles, decreased vibratory perception in the legs, and polyneuritis.

ABDOMINAL FINDINGS

The most common signs referable to the abdomen are hepatomegaly and/or splenomegaly. However, lesions in the stomach, intestines, and kidneys have been reported in a small percentage of cases.

BONE CHANGES

In 10 to 20 per cent of cases bone lesions have been reported, usually involving phalanges, metacarpals, and metatarsals. Other small bones of the hands and feet and, occasionally, the long bones may be affected. The lesions are chronic. They do not perforate or form sinuses. There may, however, be inflammation and tenderness of the overlying tissues. Deformities and painless mutilation such as occurs in leprosy are occasionally seen. (See under "Diagnosis: X-Rays.")

COMPLICATIONS

Visual symptoms may be persistent and may result terminally in total blindness. Invasion of the pituitary body has given rise to diabetes insipidus. Myx-

edema has resulted from thyroid involvements. Extensive pulmonary sarcoidosis may lead to polycythemia vera or cor pulmonale. Tachycardia, arrhythmias, and heart failure may occur with myocardial invasion. Cases have been reported in which there was involvement of the lacrimal and salivary glands, breasts, skull, testes, and epididymides.

DIAGNOSIS

Differential diagnosis includes Hodgkin's disease, lymphosarcoma, leucemia cutis, erythema induration, leucemia, mycosis fungoides, bronchiolitis fibrosa obliterans, fungus infections, tuberculosis, nodular lupus erythematosus, leprosy, and syphilis.

The correct diagnosis is often made by exclusion or biopsy of a skin lesion, lymph node, or bone lesion. However, laboratory blood studies, urine, blood chemistry, x-rays, and skin tests may add a great deal to support the diagnosis of sarcoidosis.

A. Laboratory blood work: on cases of Boeck's sarcoid will often reveal the following findings:

1. Slight hypochromic microcytic anemia.
2. Mild leucopenia—if marked, suggests splenic involvement.
3. Differential:
 - a. Eosinophilia 0 to 35 per cent—considered by some to be an index of activity;
 - b. Showers of mononuclear cells often seen if differentials are repeated frequently. Rise occurs at expense of the leucocytes.
4. Elevated sedimentation rate, this cannot be used accurately as an index of activity because hyperglobulinemia, which may not always be present, increases the rate.

B. Urine.—In a few cases a substance resembling Bence-Jones protein in its solubility at the boiling point has been found. Also occasional albuminuria and hematuria occur.

C. Blood Chemistry.

1. Total protein: Elevated, principally as a result of an increase in the globulin fraction.
 - a. Albumin—normal or slightly decreased.
 - b. Globulin—increased, often markedly.
 - c. A/G ratio—inverted, or tendency in that direction.
2. Calcium—normal or slightly elevated.
3. Phosphatase—elevated.
4. Cholesterol—normal or slightly diminished.

D. X-Rays.—

1. Lung fields: Three types of infiltration:
 - a. Peribronchial fibrosis and thickening usually extending downward symmetrically into the lower lobes.
 - b. Soft infiltration in the mid-lung fields sparing the apices.

c. Areas resembling miliary tuberculosis with a fine mottled or reticulated appearance.

There is often likely to be tracheobronchial and mediastinal lymphadenopathy of varying proportions.

In a series of cases by Katz,¹³ resolution occurred in 60 per cent in seven weeks to three years with an average of twenty-two months.

2. Bones: One may be able to see trabeculation and cyst formation in the phalanges, metacarpals, metatarsals, and other small bones of the hands and feet. Cysts are occasionally seen in the tibia, ulna, and skull. They are sharply punched-out areas with little change in the density of surrounding bone.

E. Skin Tests and Reactions.—

The old tuberculin skin reaction is usually negative even to dilutions as low as 1:100. Schaumann² states he has never seen a positive tuberculin test in uncomplicated sarcoidosis. Others have reported as high as 40 per cent positive tuberculin reactions, although of a mild degree.

Kveim¹¹ has developed an antigen produced from "sarcoid tissue" from lymph nodes ground and suspended in sterile saline with 0.5 per cent carbolic acid. When 0.1 to 0.2 c.c. of this material is injected intracutaneously a reddish brown papule appears, usually in the course of a week (sometimes it takes several weeks), in patients afflicted with Boeck's sarcoid.

This test is supposed to be specific and will not give any reaction in patients with tuberculosis or lupus vulgaris. However, not everyone is in agreement as to the specificity of this test.

PROGNOSIS

The course of sarcoidosis is usually toward spontaneous recovery and free from grave constitutional symptoms. Relapses may occur for years, however, and there may be residual induration of the parotid gland and persistent visual disturbances. Pathologic lesions heal by fibrosis, leaving atrophic scars.

Approximately 10 per cent of the patients develop clinical tuberculosis. The mortality rate has been reported as 5 per cent as the result of invasion of some vital structure.

TREATMENT

Unfortunately, no specific therapy has been found, so that treatment has remained empirical.

The common supportive measures consist of restriction of activity and a high caloric, high vitamin diet with plenty of fresh air and sunshine.

The following procedures have been attempted with varying degrees of success:

1. Ultraviolet irradiation.¹⁶
2. Roentgen and radium therapy.^{16, 17}
3. Carbon dioxide snow locally.¹³
4. Electrodesiccation of nodules.¹⁴

5. Leprolin and tubereulin injections.^{13, 16}
6. Neoarsphenamine or other arsenicals.³
7. Gold salts.¹⁴
8. Typhoid antigen.⁷
9. Iodides.⁵

SARCOIDOSIS IN CHILDREN

Thornhill⁶ has reviewed the literature until 1942. He states that sarcoidosis in children is rare, but when found usually involves the skin, lymph nodes, lungs, and bones.

Roos described a case of Boeck's sarcoid in a girl of 4 years who had lesions in the skin, liver, spleen, kidneys, lymph nodes, and brain. He cited from the literature nine other undoubted cases in which the disease occurred in children. All but two of them were over 6 years of age and had cutaneous lesions; five had cystic changes in the bone; two had enlargement of lymph nodes, and in two others there was enlargement of the mediastinal lymph nodes. Muller reported the case of a 12-year-old girl with involvement of lymph nodes, lungs, and phalanges. Naumann described two cases, one with sarcoid formation in the falx and tentorium cerebelli and the other with pulmonary involvement. Newns and Hardwick reported on a 2-year-old boy with spindle-shaped swellings of the fingers and cystic changes in the phalanges.

Although the eye is one of the likeliest sites of the disease in man,⁴ Thornhill's review of the literature has not shown this to be true in children. A recent report has been published describing sarcoidosis in siblings in two unrelated families.¹⁵

SARCOIDOSIS: ANALYSIS OF TWELVE CASES OF BOECK'S SARCOID IN CHILDREN ADMITTED TO DUKE HOSPITAL

A diagnosis of Boeck's sarcoid has been made in twelve children admitted to Duke Hospital from 1941 to 1947. Of these patients, eleven had biopsies of either lymph nodes or skin lesions. Ten of the pathologic reports came back as "typical," "suggestive of," or "consistent with" Boeck's sarcoid. One was simply reported as "chronic lymphadenitis with tubercle formation, consistent with tuberculosis or sarcoidosis." The children ranged in age between 9 and 15 years with an average age of 11.8 years. Of these young patients, 66 per cent were of the Negro race, and 75 per cent of the cases occurred in boys.

Onset of symptoms occurred between December and April for 75 per cent of the patients. The duration of active disease has been more than four months in every case. Weight loss was prevalent in 66 per cent of cases, with an average loss of some 14 pounds.

Presenting complaints of photophobia, increased lacrimation, diminution of vision, and pain in one or both eyes were given in 58 per cent of the cases. Symptoms referable to the chest, such as chronic nonproductive cough (productive later in a few cases) and exertional dyspnea, were described in 42 per cent of the cases. None of these patients had had any hemoptysis or night sweats. Only 25 per cent complained of anorexia, nausea, vomiting, or vague epigastric pains.

TABLE I. SUMMARY OF TWELVE CASES OF

CASES	AGE (YR.)	DATE OF ONSET	DURA- TION	SYMPTOMS	SKIN LESIONS	LYMPH- ADENOP- ATHY
J. R., N. F.	9	Aug. 1941	6 mo.	Pain and soreness in left eye, diminished vision in left eye	Atypical. Three scarred areas on post. aspect of rt. thigh	General- ized
A. L., W. F.	9	March 1943	18 mo.	Malaise, dizziness, low-grade, fever, nonproductive cough, back pain, and pain in both feet	None	General- ized
J. F., N. F.	9	Jan. 1942	5 mo.	Chronic cough, conjunctivitis, puffiness of eyelids, progres- sive enlargement of lacrimal, parotid, and maxillary glands	None	General- ized
E. P., N. M.	9	Dec. 1942	5 mo.	Pain in the eyes, photophobia, lacrimation, and diminution of vision	Small fine rash. Few large nodules over back & lower extrem- ities	Cervical
F. S., N. M.	11	Dec. 1942	9 mo.	Essentially asymptomatic	Healing sores & raised nodules over body	General- ized
T. P., W. M.	12	July 1941	Unknown; in Jan., 1946, de- veloped pulmo- nary tbc.	Weakness, anorexia, nausea, and vomiting, vague abdomi- nal pain	None	General- ized
W. B., N. M.	13	March 1945	8 mo.	Pain and diminution of vision in left eye and increased lacrimation, malaise, chronic productive cough	Widespread maculopap- ular & nodular lesions	General- ized
G. F., N. M.	14	April 1947	4 mo.	Photophobia, conjunctivitis, dimming of vision, epigas- tric pain	Many old healed scarred lesions	General- ized
J. T., W. M.	14	Dec. 1942	7 mo.	Slight fever and vomiting, pain in the heels and achilles tendons	None	Right submax- illary node
H. W., N. M.	14	Jan. 1942	12 mo.	Pain in eyes, photophobia, loss of close vision, exertional dyspnea, dry hacking cough	Several areas of in- creased pigmentation over chest, lower ex- tremities, & left naris	General- ized
J. G., N. M.	15	Feb. 1941	11 mo.	Dyspnea, diminution of vision in left eye, development of skin nodules	Verrucous-like growths & smaller clear lesions widely scattered	General- ized
J. G., W. M.	15	Aug. 1942	2½ yr.	Anorexia, weakness, weight loss	None	General- ized

BOECK'S SARCOID OCCURRING IN CHILDREN

TYPICAL CHEST X RAY PICTURE	BONE CYSTS	OCULAR INFLAMMATIONS	LYMPH NODE BIOPSY	FOLLOW UP
Mottling & soft infiltration with thickening about hila	None	Keratitis & iritis of left eye	"Probable Boeck's sarcoid"	Returned to clinic in Oct., 1947, for 6 yr. follow up and was found in good health, but has a residual corneal opacity in left eye
Enlarged perihilar nodes & increased lung markings	Navicular & tibia	None	None	Could not be located for 4 yr. follow up.
Diffuse nodular infiltration	None	Conjunctivitis & enlarged lacrimal glands	"Chronic lymphadenitis with tubercle formation"	For 5 yr. follow up local Pub Health Dept. reports "In good health, fully recovered, and leading normal life."
Bilateral glandular enlargement about hila & diffuse streaky process involving both lungs	Scattered in phalanges & toes	Conjunctivitis, keratitis & iritis in rt. eye	Biopsied skin lesion "suggestive of Boeck's sarcoid"	Clinically well on return to clinic for 5 yr. follow up in Sept., 1947. Residual calcified lesion evident in rt. cornea
Diffuse mottled process	Phalanges	Subcutaneous nodule in rt. upper lid, bluish flat lesions on sclerae	"Consistent with Boeck's sarcoid"	In 5 yr. follow up, letter from local physician stated boy was in good health
Bilateral hilar thickening & bronchial thickening	Questionable bone cyst in phalanx	None	"Characteristic picture of Boeck's sarcoid"	Institutionalized at N. C. State Sanatorium with rt. sided pulmonary tb. from Sept. 18, 1946. to Feb. 23, 1947. Sputum had become negative on discharge. Has subsequently developed spondylitis and is back at sanatorium pending further study.
Increased hilar nodes & mottled areas of increased density	None	Keratitis with iritis of left eye & secondary glaucoma	"Typical of Boeck's sarcoid"	Inability to locate patient prevented 2 yr. follow up.
Hilar adenopathy & some infiltration of rt. middle lobe	No studies	Keratitis & urethritis bilaterally	"Almost exclusively suggestive of Boeck's sarcoid"	Following discharge from Duke Hospital in April, 1943, was mistakenly placed in the N. C. State Sanatorium. Shortly discharged and letter from local physician states boy is clinically well.
Several areas of calcification at hila	Superior margin of left acetabulum	None	"Consistent with Boeck's sarcoid"	No 5 yr follow up obtainable
Diffuse fibrotic infiltration & enlarged tracheo bronchial nodes	None	Keratitis & iritis bilaterally	"Consistent with Boeck's sarcoid"	5 yr follow up reveals that patient has lost vision in one eye, and has continued to have visual improvement in other eye. Skin lesions have failed to clear up but cause no difficulty.
Increased size of hilar nodes & mottled areas of increased density	Suspicious areas in phalanges	Keratitis & iritis in left eye	"Typical picture of Boeck's sarcoid"	6 yr follow up reveals residual opacity in left cornea but no pulmonary or skin symptomatology according to local physician
Thickening about both hila radiating into upper & mid lung fields on left	None	Upper lids puffy, slight ptosis	"Compatible with Boeck's sarcoid"	Patient not available for 5 yr. follow up

In addition to their other symptoms 50 per cent of the patients complained of malaise, weakness, and low-grade fever. One 11-year-old Negro boy came in asymptomatic but for nodules and other skin lesions scattered over his entire body.

During hospitalization the majority of these children had a low-grade fever (often afternoon), with temperatures ranging from 37.5° to 38.8° C. Skin lesions were conspicuously absent in 42 per cent of the cases. The remainder ran the gamut from raised irregular nodules over large parts of the body to small, pigmented, atrophic scars over an extremity. No definite mucous membrane lesions were seen in any of the cases in this series. All patients showed varying degrees of lymphadenopathy. Nodes most commonly enlarged are listed in the order of frequency of involvement: anterior and posterior cervicals, axillary, inguinals, posterior auricular, occipitals, and epitrochlear. Some few patients had enlarged submaxillary and submental nodes.

Relative to the chest, only one patient (8 per cent) failed to show the typical variety of lung x-ray findings such as enlarged perihilar nodes, peribronchial fibrosis and thickening, soft or streaky infiltration of mid-lung fields, or a diffuse mottled process simulating miliary tuberculosis. This one exception showed simply several areas of calcification at the hila. Of the eleven patients with chest findings, one is known to have gone on to develop pulmonary tuberculosis with additional involvement of the lumbar spine.

Suggestive or actual bone lesions were picked up in 50 per cent of the children. These lesions were either spotty decalcification or well-circumscribed, punched-out cysts in the small bones of the hands and feet. One of these patients also had some lesions in the tibia. Another patient had a punched-out cyst in the left acetabulum.

Keratitis and iritis were present on admission in 50 per cent of the patients. Bilateral involvement was seen in 16 per cent. Three other children gave symptoms referable to the eyes. One child had subcutaneous nodules in the right upper lid, and bluish flat lesions on the sclerae. Another complained of conjunctivitis and enlarged lacrimal glands. A third child had simply puffy upper lids with slight ptosis.

Parotitis was present in only one case, or 8 per cent. The spleen was palpable in 50 per cent of the cases and the liver, in 25 per cent. No heart or central nervous system lesions were detected in this series.

Laboratory findings were of considerable aid in supporting the diagnosis in over 80 per cent of the cases. Weltmann bands were determined on seven patients and ranged from 5 to 8. Serologic tests for syphilis were uniformly negative in all cases. Agglutinations for brucellosis and typhoid were negative in the four patients on whom these tests were run. Repeated sputum examinations and gastric analyses for acid-fast organisms also failed to reveal anything of significance. Tuberculin skin tests were negative down to dilutions of 1:100. Two of the patients who remained hospitalized for a very short time failed to receive skin tests. Eosinophilia ranged from 0 per cent in three children to as high as 13 per cent. Of those with eosinophilia, the average was 6 per cent. Corrected sedimentation rates ranged from 6 to 38 mm. per hour with an average reading of 23 mm.

Blood chemistry revealed total proteins ranging from 6.6 to 9 mg. per cent with a rather even distribution. The globulin fraction was uniformly elevated, averaging 4.3 mg. per cent in ten cases.

Treatment in the majority of these children consisted of nothing more than limiting their activity and placing them on a high caloric, high vitamin diet with supplementary cod liver oil and ascorbic acid.

X-ray therapy over the cervical nodes was tried in one case, but there has been no follow-up as yet.

The patients with eye involvement were for the most part given $\frac{1}{4}$ to $\frac{1}{2}$ per cent atropine eye drops three times a day and zinc and boric acid eyewashes with compresses if needed.

CONCLUSIONS

1. Boeck's sarcoid in children has been seen in twelve out of 5,164 admissions on the pediatric service of Duke Hospital in the past six years, or an incidence of 0.23 per cent.

2. In children, Negro males are most commonly afflicted.

3. Quite typical chest findings are seen in nearly every case—92 per cent in this series.

4. Lymphadenopathy appears to be uniformly present to a greater or lesser degree.

5. Skin lesions may or may not be present; they were absent in 42 per cent in this series.

6. Pulmonary tuberculosis is a serious complication in about 10 per cent of cases with chest findings.

7. Bone cysts or spotty decalcification is suggestive confirmatory evidence in about 50 per cent of cases.

8. Keratitis and iritis, which, in the literature, were reported as being rare in children, were seen in 50 per cent of cases.

9. Uveoparotid syndrome may be quite rare in children under 15 years, there being none in this series.

10. A five-year follow-up on this series of patients indicates that sarcoidosis may run an entirely benign course except for residual lesions of the cornea and/or uveal tract in those patients originally afflicted with ocular disease.

11. There are no known fatalities among this series of twelve children.

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FURTHER OBSERVATIONS CONCERNING HYPOFUNCTION OF THE ADRENALS DURING EARLY LIFE

"SALT AND WATER" HORMONE DEFICIENCY

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IN A recent publication,¹ a theory of physiologic hypofunction of the adrenal glands during early life was presented. The possibility that latent hypoadrenalism of a temporary nature may present clinical manifestations during early infancy has been long entertained but has lacked a demonstration sufficiently convincing to be accepted.

Only a few publications were found which describe the use of adrenal hormones during early infancy.²⁻⁵ In these reports the adrenal hormones were used empirically.

With the exception of four cases of macrogenitosomia,^{9-11a} patients with Addison's disease,¹² a few reports of adrenal tumors, and cases of Waterhouse-Friderichsen syndrome, there have been, to my knowledge, no cases of adrenal insufficiency during infancy which have been definitely proved.

The purpose of this paper is threefold:

1. To re-emphasize the necessity for the pediatrician to acquaint himself with the life-sustaining functions of the adrenal glands; and to think of the possibility of temporary hypofunction of these glands when dealing with infants during early life who present symptoms of protracted gastrointestinal disturbances, who fail to gain weight, who have an unexplained tendency to dehydration, and who respond unsatisfactorily to the accepted therapeutic measures.

2. To present cases which I think demonstrate adequate proof of the existence of a fractional and transitory disturbance in adrenal function.

3. To describe a syndrome which is characteristic of this deficiency.

The patients described in the following case reports present symptoms of vomiting, failure to gain weight, and periods of unexplained dehydration accompanied by changes in the blood chemistry that are commonly associated with adrenal insufficiency. Each patient has had one or more hospitalizations, which clearly revealed the need of adrenal hormone therapy. A brief summary precedes the detailed report of each case.

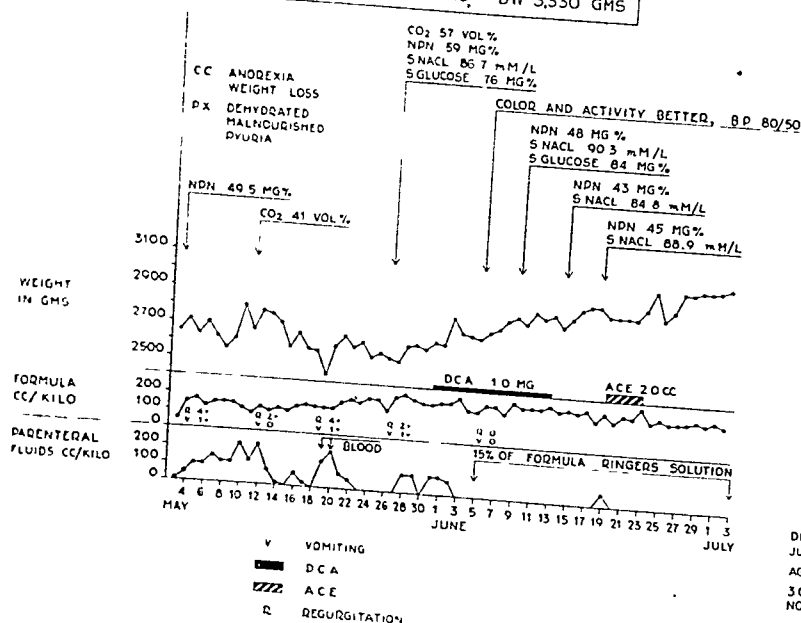
CASE REPORTS

CASE 1.—G. T., a white male infant, aged 3 weeks, was admitted to St. Louis Children's Hospital May 3, 1945, because of anorexia and persistent loss of weight. Frequent administration of parenteral fluids was required to main-

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(PART 1)

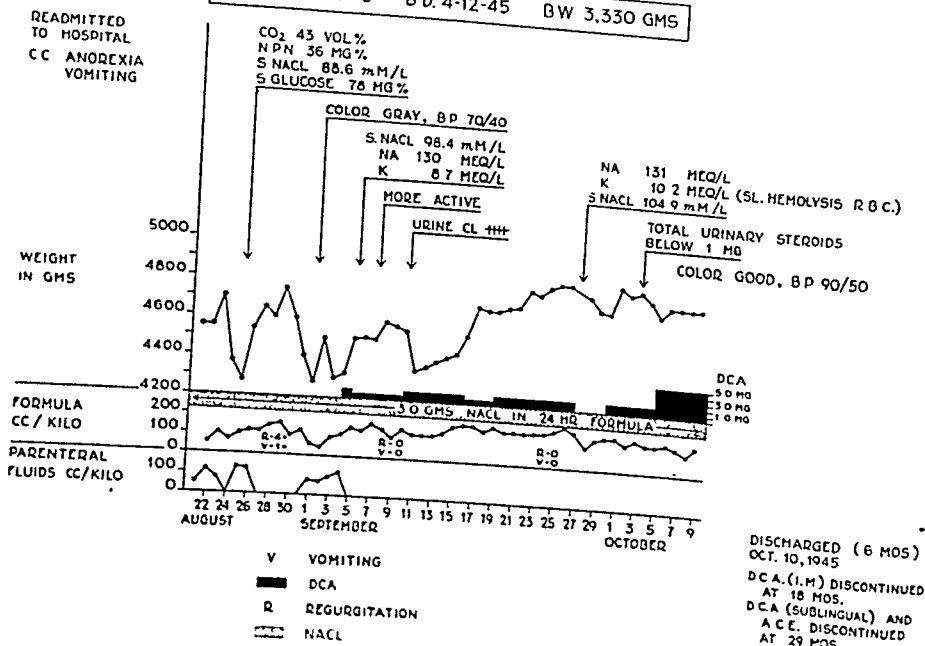
CASE #1 GT ♂ BD 4-12-45, BW 3,330 GMS



A.

(PART 2)

CASE #1 GT ♂ BD 4-12-45 BW 3,330 GMS



B.

Fig. 1. A and B.—Graphic record, Case 1.

tain hydration. After three weeks of hospital care the weight was the same as on entry. Immediately following the institution of D.C.A.* therapy, there was a steady weight gain and no further need of parenteral fluids. The addition of extra electrolyte to the formula resulted in a still more rapid gain in weight. Administration of A.C.E.† produced a similar response. For one month the patient did well with only the addition of 3 Gm. of table salt to the formula. He was again seen at 4 months of age, because of vomiting, refusal of food and rapid loss of weight. As on the previous hospital admission, serum carbon-dioxide combining power and sodium chloride were moderately reduced and the nonprotein nitrogen elevated. The serum sodium was low and the potassium increased. The addition of extra salt to the formula at this time

TABLE I. FOLLOW-UP OF CASE 1

DATE	AGE (MO.)	D.C.A. (MG.)	NaCl (GM.)	WEIGHT (GM.)	REMARKS
1945 10/10	6	5.0 daily	3.0	4,760	Discharged from hospital. General condition good.
11/14	7	5.0 daily	3.0	7,020	Phys. exam. neg. except "soapy tissue." Ht. 66.9 cm., teeth 0/2. B.P. 100/60. S.NaCl. 112 mM/L. Na. 143 meq./L. K. 7.0 meq./L. Advice: 5.0 mg. D.C.A. every other day.
1946 1/3	9	5.0 every other day	3.0	8,160	Phys. exam. neg. Ht. 69 cm. Crawling. No edema. B.P. 98/62. Advice: discontinue D.C.A. (4 unsuccessful attempts.)
6/6	14 (Three attempts to discontinue D.C.A.)	3.0 daily	2.0	10,560	Phys. exam. neg. Walking 1 mo. Teeth 3/2. B.P. 96/60. No edema. "Soapy skin." Further reduction D.C.A. results in constipation, irritability, anorexia, need to relearn.
10/16	18	3.0 daily	2.0	12,500	Phys. exam. neg. Ht. 85 cm. Teeth 6/6. B.P. 120/60 (crying). Co. 52 vols. %. N.P.N. 27 mg. %, S. NaCl. 102 mM/L. S. glucose 90 mg. % I.V. pyelograms neg. Advice: discontinue D.C.A. Subling. Cortate 2.0 mg. t.i.d.—reduce if possible. A.C.E. 5 c.c. weekly.
		HOSPITAL			
1947 3/26	23	2.0 sub- ling. 2x day	3.0	13,560	Phys. exam. neg. "Soapy skin." B.P. 110/70. No edema. Talking. Advice: 2.0 mg. subling. Cortate every other day. 2.5 c.c. A.C.E. weekly.
6/25	26	2.0 sub- ling. every other day	3.0	14,400	Doing well. Advice: 2.0 mg. subling. Cortate every 3 days. 2.5 c.c. A.C.E. weekly.
8/26	28	2.0 sub- ling. every three days	3.0	14,880	Phys. exam. neg. Ht. 93 cm. "Soapy tissue." B.P. 102/60. Advice: 2.5 c.c. A.C.E. every other week. Discontinue subling. Cortate if possible.
9/4	29	None	None	15,840	Has been well since. "Soapy skin" gradually disappeared.

*Desoxycorticosterone acetate, "Doca."

†Adrenal Cortex Extract, or whole beef extract. Each cubic centimeter is obtained from not less than 40 Gm. of adrenal gland and contains not less than 50 dog units or 2.5 rat units. This extract is water soluble. It was supplied by The Upjohn Company, Kalamazoo, Mich.

was of no real benefit; however after D.C.A. was started there was an immediate increase in food intake, a steady gain in weight, and a gradual return of the blood chemistry to normal.

Numerous attempts were made to discontinue the adrenal steroid and reduce the salt intake, but this invariably resulted in constipation, irritability, listlessness, refusal of food, and loss of weight. When properly regulated, the child appeared perfectly normal, with the exception of a soft, soapy texture of the skin and subcutaneous tissues, which was evident from the age of 7 months. The blood pressure remained normal, and there was no evidence of edema at any time during the course of D.C.A. and salt therapy. The total steroids excreted in the urine in twenty-four hours were below 10 mg.

At 18 months of age, the intramuscular injections of desoxycorticosterone acetate were discontinued and sublingual steroid Cortate* substituted. A.C.E. was injected at weekly intervals because it was thought at that time that the possibility of atrophy of the adrenal glands was most likely. It was possible, however, to reduce gradually the sublingual D.C.A. and A.C.E., and at 29 months of age to discontinue the hormones and extra salt. Although it has been many months since hormone therapy was discontinued, the child has remained well and his general physical and mental growth are normal for his age. The skin and subcutaneous tissues have gradually lost their soft, soapy texture.

DETAILED CASE REPORT

G. T. was born April 12, 1945. The birth weight was 3,330 Gm. He was full term, delivery was normal, and there was spontaneous cry and respiration. The family history revealed no evidence of endocrine disorders. The parents are large and healthy. Two male siblings have been normal and healthy.

Because of a steady loss of weight and tendency to regurgitate since birth, he was admitted to St. Louis Children's Hospital on May 3, 1945. The patient was thin, malnourished, and moderately dehydrated, but was active and had a good cry. The weight was 2,650 Gm. or 680 Gm. under birth weight. The skin was clear. There was a hypospadias associated with undescended testes. Laboratory data: Hemoglobin 17.7 Gm., white blood count 15,500, stabs 6, segmentals 18, lymphocytes 42, monocytes 4. Wassermann and tuberculin tests were negative. The urine contained numerous pus cells. The carbon dioxide combining power was 40 volumes per cent and the nonprotein nitrogen 49 mg. per cent. The provisional diagnoses were: pyuria, malnutrition, and feeding problem. Following reports that *Bacillus coli* and staphylococci were cultured from the urine, penicillin and sulfadiazine therapy was begun. Five days later the urine was clear and sterile. Despite an intake of approximately 150 c.c. per kilogram per day of the usual evaporated milk and Karo formula, the child continued to lose weight, and on May 8, five days after admission, the weight was 2,550 Gm. Parenteral fluids in the form of equal parts of 10 per cent glucose and lactate Ringer's were necessary in the amounts of 100 to 200 c.c. per kilogram per day, to prevent clinical evidence of dehydration. On May 11, eight days after entry, the weight had increased to 2,670 Gm., the carbon dioxide combining power was 31 volumes per cent, and the nonprotein nitrogen 35 mg. per cent. On May 16 fluid administration was discontinued, and during the next five days the weight dropped to 2,450 Gm. even though the intake of formula averaged around 150 c.c. per kilogram per day. Up to this time, there had been a minimal

*Each cubic centimeter contains 10 mg. desoxycorticosterone acetate in a solution of propylene glycol containing 20 per cent dehydrated alcohol, U.S.P. Supplied by the Schering Corporation, Bloomfield, N. J.

amount of regurgitation of food, and no diarrhea. For the next two weeks, the weight remained around 2,600 Gm., little influenced by the increased intake of formula to 200 c.c. per kilogram per day and the frequent administration of parenteral fluids. During this period there was more regurgitation. Three weeks after admission to the hospital, the carbon-dioxide combining power had gradually risen to 57 volumes per cent, the nonprotein nitrogen was 59 mg. per cent, serum sodium chlorides 86 mM per liter, and true serum glucose 76 mg. per cent.

On June 1, 1945, after one month of hospitalization and no appreciable improvement, daily injections of 1.0 mg. of D.C.A. were begun. For the next five days there was a gradual weight gain to 2,700 Gm., and parenteral fluids were no longer required. Because of the slow gain in weight about 15 per cent of the formula was made up with Ringer's solution. Seven days later the weight was 2,850 Gm., a gain of 150 Gm. without subcutaneous fluid therapy. The formula intake remained around 200 c.c. per kilogram per day during this period, the tendency to regurgitate entirely disappeared, and the baby appeared more contented. On June 12 the D.C.A. was discontinued, but the Ringer's solution was left in the formula. There was a temporary weight loss and then a gradual gain to 2,920 Gm. six days later. Following this the weight decreased and again there was need for parenteral fluid therapy. On June 20, A.C.E. was begun, and four days later the weight had increased to 3,000 Gm. There was only a temporary weight loss following the withdrawal of Adrenal Cortex Extract. On July 3, after two months of hospitalization, the patient was discharged weighing 3,090 Gm. The mother was instructed to put 3.0 Gm. of table salt in the formula.

He was again seen at four months of age. The weight was 4,800 Gm., blood pressure 96/60, serum sodium chloride 97.5 mM. per liter, nonprotein nitrogen 37.0 mg. per cent, and fasting glucose 100 mg. per cent. He had done quite well on just the addition of salt to the formula. On Aug. 17, 1945 he was again admitted to the hospital because of anorexia, irritability, and vomiting. The baby was listless, appeared nauseated, and the skin was a dirty gray color. The weight was 4,550 Gm. There was no evidence of infection. The urine was clear. Hemoglobin was 11.3 Gm.; white blood count 11,500; eosinophiles 3, stabs 2, segmentals 25, lymphocytes 68, monocytes 2. Since there was little evidence of dehydration he was placed on the usual stock formula plus 3.0 Gm. sodium chloride and observed. Four days later the weight was 4,280 Gm., a loss of 270 Gm. He became dehydrated, refused most of the formula, and the dirty gray color was more pronounced. The carbon-dioxide combining power was 43 volumes per cent, nonprotein nitrogen 36 Mg. per cent, serum sodium chlorides 88.6 mM per liter, and fasting serum glucose 78 mg. per cent. The salt was removed from the formula. During the next few days large amounts of parenteral fluids were required (see Fig. 1B). The intake of food gradually increased, and by August 29 the weight was 4,750 Gm. Parenteral fluid therapy was then discontinued, and during the next four days there was a loss of 470 Gm. despite the intake of 100 to 150 c.c. of formula per kilogram per day. During this period regurgitation and occasional vomiting recurred. The child then became very difficult to feed. On September 4, intramuscular injections of D.C.A. were started, and 3.0 Gm. of table salt were added to the formula. On September 5 the serum sodium chloride was 98.4 mM per liter, serum sodium 130 meq. per liter, and serum potassium 8.7 meq. per liter. The weight was 4,330 Gm. before therapy. For the next five days 1.0 mg. D.C.A. was administered daily, and the weight increased to 4,550 Gm., a gain of 220 Gm. in five days. The infant was more active, ate better, and regurgitation disappeared. For the next few days despite the injections of 1.0 mg. D.C.A. daily, there was a persistent weight loss; the child remained active, looked well, and did not regurgitate, but the appetite was poor. D.C.A. was increased to 2.0 mg. daily, resulting in a rapid return of appetite and weight. On September 8 the hemoglobin was 10.8 Gm.; white blood count 8,350; eosinophiles 4, stabs 9, segmentals 28, lymphocytes 55, monocytes 4. For the next two weeks the patient was quite well, there was no need of parenteral fluid therapy, and the food intake varied from 120 to 210 c.c. per kilogram per day. D.C.A. was discontinued for three days. Immediately there was a decrease in appetite and a weight loss of 220 Gm. even though the salt intake remained constant. Individual urine specimens revealed large amounts of chlorides. On September 27, while the child was receiving salt and

D.C.A., the serum sodium chloride was 105.9 mM per liter, serum sodium 131 meq. per liter, serum potassium 10.2 meq. per liter (slight hemolysis of the red blood cells). The twenty-four hour total steroid content of the urine was below 1.0 mg. per cent, according to Dr. Willard Allen.* On October 2, a gradual tendency to lose weight was evident, and the D.C.A., the serum sodium chloride was 105.9 mM per liter, serum sodium 131 meq. per liter, on October 10, at 6 months of age. The mother was instructed to continue the daily injections of 5.0 mg. D.C.A. and add 3.0 of table salt to the formula.

He was again seen on Nov. 14, 1945, at 7 months of age. He had progressed normally, could sit erect, had two teeth, was eating well, and had gained to 7,020 Gm. The height was 66.8 cm. The "dirty" color of the skin had disappeared. The skin and subcutaneous tissues presented a slightly thickened and soapy feel. During the month interval the dose of D.C.A. and salt had remained unchanged. The serum sodium chloride was 112 mM. per liter, serum sodium 143 meq. per liter, and serum potassium 7.0 meq. per liter. The mother was advised to give 5.0 mg. D.C.A. every other day and continue 3.0 gm. table salt in the milk.

On Jan. 3, 1946, at 9 months of age, the child looked fine, was pulling up, had a good appetite and color, and in every respect appeared normal. There was no evidence of edema, the blood pressure was 100/60, the height was 68.7 cm., and the weight 8,370 Gm. A diligent attempt was again made to discontinue the D.C.A. because at this time I was definitely worried about the possibility of producing atrophy of the adrenal glands. For the next five months the mother tried repeatedly to discontinue the injections. It was found that the steroid could be reduced to 3.0 mg. daily, but when a further reduction of the dose was attempted, the child became irritable, gradually lost appetite, was constipated, and had difficulty in remembering. On June 6, 1946, at 14 months of age, he was seen running around, had four teeth and appeared normal. The weight was 10,560 Gm., the height 77.5 cm. There was no evidence of edema; blood pressure was 96/58; the heart was normal. The salt was reduced to 2.0 Gm. per day. During the next four months three concerted attempts were made to discontinue D.C.A.; however the dose could be lowered only to 2.0 mg. and the salt to 2.0 Gm.

On Oct. 16, 1946, at 18 months of age, he was admitted to the hospital for regulation on sublingual D.C.A., thus eliminating the need for daily intramuscular injections. At this time he once more appeared perfectly normal, with the exception of a slightly thickened, soaplike texture of the skin. There were ten well developed teeth, the height was 85 cm., weight 12,500 Gm., blood pressure 120/70 (while crying), no edema. The carbon-dioxide combining power was 52 volumes per cent, nonprotein nitrogen 27 mg. per cent, serum sodium chloride 102.3 mM per liter, and fasting serum glucose 90 mg. per cent. The hemoglobin was 12.8 Gm.; white blood count 15,000; stabs 3, segmentals 45, lymphocytes 50, monocytes 2. Intravenous pyelograms were normal. He was discharged a few days later on 2.0 mg. Cortate sublingually three times daily, plus 2.0 Gm. sodium chloride. The mother was instructed to make every effort to reduce this dose gradually and if possible to eliminate it entirely. In addition, he was to receive 3.0 cc. Adrenal Cortex Extract weekly and the salt to be removed from the milk, if possible. For the next five months the child had many respiratory infections associated with otitis media and cough, for which sulfadiazine was prescribed. By March 26, 1947, at 2 years of age, it was possible to decrease the sublingual dose of D.C.A. to 2.0 mg. every other day, but the salt remained the same. The weight was 13,560 Gm., height 87.5 cm., blood pressure 100/70, appearance and activity normal.

He was again seen on June 25, 1947, at 26 months of age. He was talking, weighed 14,400 Gm., and looked normal. Sublingual D.C.A. had been decreased to 2.0 mg. every three days and the A.C.E. to 2.5 cc. weekly. Two months later the height was 93.7 cm. and weight 14,880 Gm. There was no desire for extra salt, nor was it given, but the mother thought it was necessary to continue sublingual Cortate 2.0 mg. every three days. The blood pressure was 102/60.

On Sept. 4, 1947 it was possible to discontinue the sublingual D.C.A. and A.C.E. He continued to have a fair number of respiratory infections, but handled them more like the

*Professor of Obstetrics and Gynecology, Washington University School of Medicine.

normal child. Recently he had an intestinal upset with vomiting and diarrhea, such as was prevalent in the family and neighborhood. He recovered promptly, without the need of hormone or salt therapy. At no time during the course was the blood sugar abnormally low, nor were there symptoms suggestive of hypoglycemia. He was last seen in February, 1948. The skin and subcutaneous tissue had lost the soapy, thick feel. Outside of the hypospadias and undescended testes, the child is normal in every respect.

CASE 2.—D.U., a white, full-term male infant, was apparently normal at birth. Because of frequent vomiting and the appearance of gastric waves, a diagnosis of pyloric stenosis was made and operation was performed at 14 days of age. No definite pyloric tumor was found. He was admitted to St. Louis Children's Hospital at 16 days of age because of persistent vomiting. The patient was alert, moderately dehydrated, very irritable, and appeared nauseated. The genitals were normal. The serum carbon-dioxide combining power was moderately reduced. Large amounts of parenteral fluids were required to maintain hydration. Despite the frequent appearance of intestinal patterns and occasional gastric waves, investigation of the gastrointestinal tract revealed no evidence of obstruction. Thickened feedings, gavage, and changes of formula produced no substantial results. After one month of hospitalization he was discharged with the diagnosis of "feeding problem." A few days later he was readmitted in a state of collapse. Daily parenteral fluids were again required to prevent clinical signs of dehydration. The infant continued to vomit at frequent intervals. After two months of hospitalization with no apparent improvement, the possibility of low adrenal function was considered. The carbon-dioxide combining power was low, nonprotein nitrogen elevated, and serum sodium chloride reduced. Large amounts of chlorides were found in the urine, even during periods of dehydration. After regulation on extra salt and D.C.A. there was immediate improvement and no need for parenteral fluids (see Fig. 24). Attempt at regulation on sublingual Cortate was unsuccessful. The patient remained well on this therapy, gained weight, and did not vomit. At 6 months of age the intramuscular D.C.A. was gradually discontinued and sublingual D.C.A. substituted (see Fig. 2B).

He got along well for one month until the onset of otitis media, which was followed by vomiting, irritability, anorexia, constipation, and the need for re-hospitalization. He was again found in mild acidosis and a moderate degree of collapse. The serum sodium chloride and serum sodium were reduced, the nonprotein nitrogen and serum potassium elevated, and the blood sugar was normal. It was necessary to resume daily intramuscular injections of D.C.A. It was not until 11 months of age that it was possible to reduce appreciably the D.C.A., and at 13 months of age there was no further need for hormone or salt therapy. Since discontinuing adrenal therapy, the patient has had two severe illnesses, one associated with vomiting, but he has recovered promptly on his own.

DETAILED CASE REPORT

D. U. was born on June 13, 1946; the birth weight was 3,770 Gm. He was the first child, delivery was normal, and cry and respiration were spontaneous. After the first few

(PART 1)

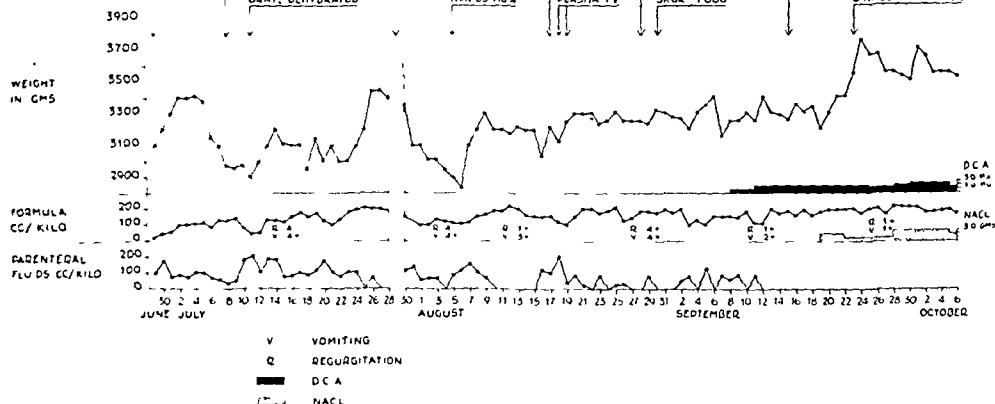
CASE #2 DU ♂ BD 6 13-46 BW 3,770 GMS

CC VOMITING DC SINCE BIRTH
OPERATED FOR PYLODIC STENOSISPX DEHYDRATED
STITCH ABSCESS
GASTRIC WAVES
7 ALKALOSISHOME 2 DAYS
VOMITING
LISTLESS
IRRITABLENDN 55 MG%
CO₂ 43 VOL%
S GLUCOSE 80 MG%COLLAPSE, "DIRTY" GRAY COLOR
ANHYDREMIC
UNABSORBED FLUIDS

GI SERIES

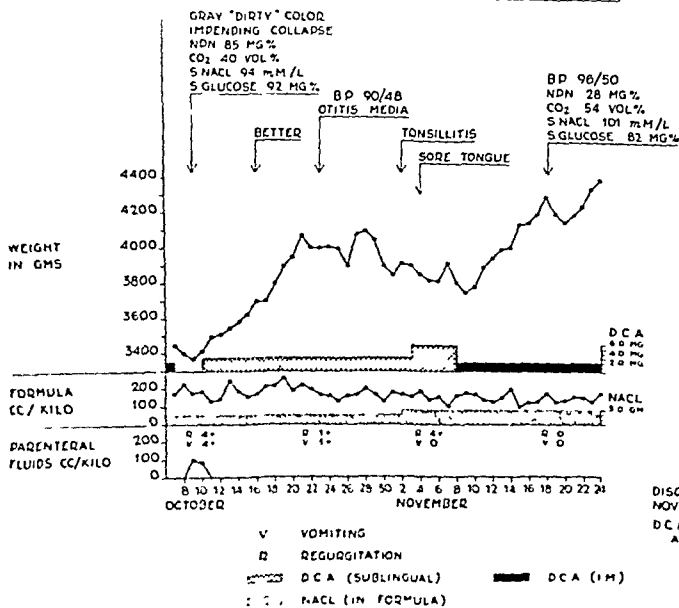
NDN 49 MG%
CO₂ 42 VOL%
S NAEL 98 MM/L
URINE CL 4+
SRGG 1006

BETTER

BP 108/52
NDN 38 MG%
CO₂ 46 VOL%
S NAEL 106 MM/L

(PART 2)

CASE #2 DU ♂ BD 6 13-46 BW 3,770 GMS

DISCHARGED (5 1/2 MOS)
NOV 23, 1946
DCA DISCONTINUED
AT 13 1/2 MOS

B.

Fig. 2, A and B.—Graphic record, Case 2.

days of life he began to spit up breast milk immediately after feeding. From the fifth day on he vomited almost every feeding, and at times the vomiting was projectile. On June 21 a barium meal revealed delay in emptying time; a large amount of the barium was still in the stomach after six hours. Gastric waves were occasionally noted and at 14 days of age he was operated on for pyloric stenosis but nothing definite was found. He continued to vomit following operation and was therefore admitted to St. Louis Children's Hospital on June 29, 1946. Physical examination revealed a moderately dehydrated but alert infant. Because he was thought to be in alkalosis, the carbon dioxide combining power was determined and found to be 48 volumes per cent. A small stitch abscess was found near the operative wound. For the next couple of weeks he required between 150 and 200

TABLE II. FOLLOW-UP OF CASE 2

DATE	AGE (MO.)	D.C.A. (MG.)	NaCl (GM.)	WEIGHT (GM.)	REMARKS
1946 11/23	5½	2.0 daily	2.0	4,360	Discharged from hospital, condition good.
12/6	6	2.0 daily	2.0	5,160	Phys. exam. neg. No vomiting. B.P. 90/50. Advice: Continue same therapy.
12/31		2.0 daily	2.0		Discontinue I. M. D.C.A., substitute subling. D.C.A. 1.5 mg. t.i.d.
1947 1/13	7	1.5 subling. t.i.d.	2.0	6,930	Phys. exam. neg. Doing well. No vomiting.
1/23		1.5 subling. t.i.d.	2.0	6,420	C.C. constipation, anorexia, irritable, vomiting. Phys. exam: T. 38.2° C. Rt. O.M. Dehydrated, gray, near collapse. CO ₂ 26 vol. %, N.P.N. 37 mg. %. S. NaCl 98 mM/L. S. glucose 70 mg. %. R 10 c.c. A.C.E. - 5% glucose in normal saline sol. I.V., 2.0 mg. D.C.A. - 2.0 Gm. NaCl daily. 1/27/47—S. Na. 127 meq./L. K. 5.3 meq./L.
		HOSPITAL			
1/31	7½	2.0 daily	2.0	6,500	Discharged. Condition good.
2/13	8	1.0 daily	2.0	6,960	Phys. exam. neg. No vomiting. B.P. 94/50.
3/12	9	0.5 daily	2.0	8,220	Phys. exam. neg. Ht. 65 cm. (parents small). B.P. 104/60. No edema. Advice: 0.25 mg. D.C.A. daily and discontinue in 2 wk.
4/1	9½	None	2.0	8,790	Phys. exam. neg. 10 days later irritable, anorexic, vomited. Wt. 8,200 Gm.
4/12	10	2.0	3.0	7,740	Phys. exam.: gray, dehydrated, mild collapse. B.P. 65/50. Rt. O.M. S. Na. 128 meq./L. K. 5.2 meq./L. CO ₂ 47 vol. %, N.P.N. 42 mg. %. R A.C.E., glucose and normal saline sol. I.V., 2.0 mg. D.C.A. - 3.0 Gm. NaCl daily.
		HOSPITAL			
4/27	10½	2.0 daily	3.0	8,040	Discharged.
5/27	11½	0.5 daily	2.0	9,300	Phys. exam. neg. Ht. 68 cm. Excellent health. "Soapy tissue." Advice: gradually reduce D.C.A.
6/25	12½	0.5 every other day	2.0	9,870	Phys. exam. normal. Ht. 70.5 cm. Walking. B.P. 96/54. Advice: 0.5 mg. D.C.A. every 3 days, then discontinue.
7/20	13½	None	2.0	10,200	Phys. exam. neg. Ht. 72.5 cm. B.P. 100/60. No complaints.
10/24	16½	None	None	10,800	Normal. Ht. 75 cm. No NaCl for 2 wk. S. NaCl. 102 mM/L. CO ₂ 56 vol. %. S. glucose 74 mg. %. Normal since.

c.c. of parenteral fluids per kilogram per day to maintain hydration. He was a very reluctant feeder, needed encouragement, and frequently regurgitated the formula immediately after taking. Gavage and then thickened feedings were tried, with only temporary improvement. One day he was found to be ashen gray, in a state of mild collapse, but he responded fairly well to intravenous and subcutaneous fluids. Barium meal revealed nothing except a moderately slow emptying time of the stomach. Eventually he was able to get along without parenteral fluids. By July 24 he was much better, despite the persistent tendency to regurgitate. He was discharged on July 28, one month after admission, weighing 3,400 Gm., a gain of only 220 Gm. Twenty-four hours after discharge, following a short period of constant vomiting, he was readmitted in a state of collapse. The vomitus did not contain bile, and the stools were normal. There was no evidence of infection. The weight was 3,120 Gm. He was dehydrated but mentally alert. Intravenous glucose and subcutaneous fluids consisting of equal parts of 10 per cent glucose in lactate Ringer's solution were given for the next few days, in amounts varying from 100 to 150 c.c. per kilo. Vomiting continued, and on August 6 the weight had dropped to 2,890 Gm. The nonprotein nitrogen was 65 mg. per cent. Low adrenal function was not seriously considered at this time. From August 6 to August 18, despite formula intake of 150 to 200 c.c. per kilogram and frequent injections of parenteral fluids, the weight had increased to only 3,100 Gm. On August 18 he was again found in a state of collapse and dehydrated, and the subcutaneous fluids which had been given a few hours previously were not absorbed. The carbon-dioxide combining power was 13 volumes per cent. Plasma was administered intravenously for the next few days, in an effort to restore the blood volume. From August 22 to September 6 the weight remained around 3,250 Gm. despite good formula intake and the giving of parenteral fluids. On August 30, carbon dioxide combining power was 42 volumes per cent, serum sodium chloride 97.8 mM per liter, nonprotein nitrogen 48 mg. per cent, and the serum glucose 100 mg. per cent. The urine was loaded with chlorides. On September 9, 1.0 mg. of D.C.A. was given intramuscularly and three days later increased to 2.0 mg. daily. For the following nine days there was less tendency to regurgitate, and parenteral fluid therapy was required only once. Although the formula intake remained around 150 to 200 c.c. per kilo, the weight had increased only 100 Gm. On September 19, 2.0 Gm. table salt were added to the formula. In six days the weight increased 390 Gm. On September 23, the carbon dioxide combining power was 10 volumes per cent, serum sodium chloride 106 mM per liter, nonprotein nitrogen 38 mg. per cent, and serum glucose 129 mg. per cent. The D.C.A. was decreased to 1.5 mg. and salt to 1.0 Gm. This was followed by a gradual weight loss of 200 Gm. It was found that 3.0 Gm. salt and 2.0 to 2.5 mg. of D.C.A. were necessary to keep the patient from losing weight without the administration of fluids. During this entire period there was still some regurgitation, but it was not as pronounced and had improved remarkably since the institution of hormone therapy. The possibility of a partial high intestinal obstruction was still entertained. On October 8, D.C.A. was discontinued, and the weight immediately dropped to 3,380 Gm. Lipo-Adrenal Cortex* was injected intramuscularly, 0.5 c.c. daily for the next five days. After the second day the patient was found in impending shock; the carbon-dioxide combining power was 10 volumes per cent, nonprotein nitrogen 85 mg. per cent, serum glucose 92 mg. per cent. The blood pressure was 70/30. In addition to the Lipo-Adrenal Cortex, 2.0 mg. of sublingual Cortate was begun, and by October 13 the weight had increased 180 Gm. The pork extract was discontinued and the patient left on 3.0 mg. D.C.A. sublingually. On October 15 he was much better; the weight was 3,700 Gm., food intake had increased to around 180 c.c. per kilogram, and for five days there had been no need of parenteral fluids. From this time on there was a general improvement and a gradual weight gain to 4,100 Gm. by October 28. He began to spit out the sublingual D.C.A., and the tissue beneath the tongue and pharynx became inflamed. This redness did not disappear until the sublingual Cortate was discontinued on November 8. The weight gradually

*Lipo-Adrenal Cortex, or pork extract. Each cubic centimeter contains 40 R. U. Each cubic centimeter is equivalent to 2 mg. of 11-hydroxy-17-dehydrocorticosterone or 4 mg. of corticosterone. This extract is put up in oil. It was supplied by the Upjohn Company, Kalamazoo, Mich.

decreased and regurgitation was accelerated during the period when the steroid was spit out. On November 8, 2.0 mg. intramuscular D.C.A. were begun. Two grams of salt were still in the formula. There was a consistent weight gain and obvious general improvement from this time on. On November 23, five days later, the weight had increased to 4,400 Gm., the carbon-dioxide combining power was 53 volumes per cent, serum sodium chloride 102 mM per liter, nonprotein nitrogen 24 mg. per cent. The blood pressure was 90/50. The patient was discharged on November 23, at 5 months of age. He was given the usual evaporated milk formula for age, large amounts of vitamins, including 100 mg. vitamin C daily, plus small amounts of cereals, vegetables, and fruits. The mother was instructed to put 2.0 Gm. of table salt in the formula and give 2.0 mg. D.C.A. intramuscularly per day. By December 6 the weight was 5,100 Gm. The child had been perfectly well, and there was no further regurgitation. On December 31 the intramuscular D.C.A. was discontinued, and sublingual D.C.A., 1.5 mg. three times per day, was started.

He was seen again on Jan. 13, 1947 and was doing fine. The weight was 6,930 Gm. The sublingual D.C.A. was reduced to 1.5 mg. twice daily. Ten days later he was irritable, began to cut down on food, became constipated, and then vomited. He was admitted to the hospital, where it was found he had an upper respiratory infection and acute otitis media. His color was gray. The carbon-dioxide combining power was 35 volumes per cent, and nonprotein nitrogen 37 mg. per cent. The blood pressure was 88/50. A diligent effort was made for regulation without the use of D.C.A., but this nearly led to collapse. On January 28 the carbon-dioxide combining power dropped to 26 volumes per cent, and the patient resumed the tendency to vomit. There was no diarrhea. The ear infection rapidly cleared with penicillin and sulfadiazine. During the period of collapse the blood sugar was 70 mg. per cent, and the urine was alkaline and loaded with chlorides. He was given 5.0 c.c. of Adrenal Cortex Extract intravenously in equal parts of 10 per cent glucose and normal saline solution. Intramuscular D.C.A. was again started. On January 27 before intramuscular D.C.A. was resumed, the serum sodium was 127 meq. per liter, serum potassium 5.3 meq. per liter. He was discharged from the hospital on January 31, weighing 6,500 Gm. with instructions to continue 2.0 mg. D.C.A. and 2.0 Gm. salt. On February 13, at 8 months of age, the weight was 6,900 Gm. and he looked perfectly normal, was pink, active, and cheerful. The growth and development were normal for age, with the exception of length, which was only 65 cm. There was no edema. D.C.A. was reduced to 1.0 mg. per day, and the salt was kept the same. At 9 months of age the weight had increased to 8,220 Gm., the blood pressure was 90/60, and D.C.A. had gradually been decreased to 0.5 mg. The child was pulling up, quite active, and appeared normal in all respects. One week later the D.C.A. had been decreased to 0.25 mg. daily. On April 1 the weight was 8,790 Gm. The D.C.A. was discontinued, and the salt was increased to 3.0 Gm. daily. Nine days later the child became irritable, cut down on his food, and the weight decreased to 8,200 Gm. He was given sublingual cortate, 1.5 mg. three times a day, but continued to go downhill. On April 12 he again required hospitalization. The weight on this admission was 7,740 Gm., a loss of over 1,000 Gm. in twelve days. There was a return of the dirty gray color and a spontaneous drainage of the right ear. Blood pressure was 65/50. Five cubic centimeters of adrenal cortex extract in 5 per cent glucose in normal saline were given intravenously. The serum sodium was 128 meq. per liter, serum potassium 5.17 meq. per liter, nonprotein nitrogen 42 mg. per cent, carbon-dioxide combining power 47 volumes per cent, and serum glucose 75 mg. per cent. Daily injections of 2.0 mg. D.C.A. were resumed; usual doses of penicillin and sulfadiazine resulted in a rapid clearing of the otitis media. He was discharged on April 27, weighing 8,040 Gm. with instructions to his mother to put 3.0 Gm. of salt in the formula and continue 2.0 mg. D.C.A. intramuscularly. The child did well at home and by May 27, one month later, the dose of D.C.A. could be reduced to 0.5 mg. daily, plus 2.0 Gm. of salt. The weight at this time was 9,300 Gm., height 68 cm., and blood pressure 110/70. His general condition was excellent. By June 25 the dose of D.C.A. could be reduced to 0.5 mg. every other day, plus 2.0 Gm. salt. The weight was 9,870 Gm., height 70 cm., and he was normal mentally and physically. By July 20, at 13 months of age, the D.C.A. could be discontinued.

When seen again one month later the weight was 10,200 Gm, and the child was walking and appeared normal in every respect. Extra salt was no longer required. On October 24 the weight was 10,800 Gm, height 75 cm, blood pressure 100/60, serum sodium chloride 102 mM per liter, nonprotein nitrogen 24 mg. per cent, carbon-dioxide combining power 36 volumes per cent, and serum glucose 74 mg. per cent. During the second hospital admission urine was collected for total steroid content. Imperceptible amounts were reported by Dr Willard Allen's laboratory. He recently had an episode of fever associated with otitis media, which responded satisfactorily to sulfadiazine. He had an attack of vomiting which was thought to be due to a virus infection. The child recovered from both of these episodes without the resumption of hormone or salt therapy.

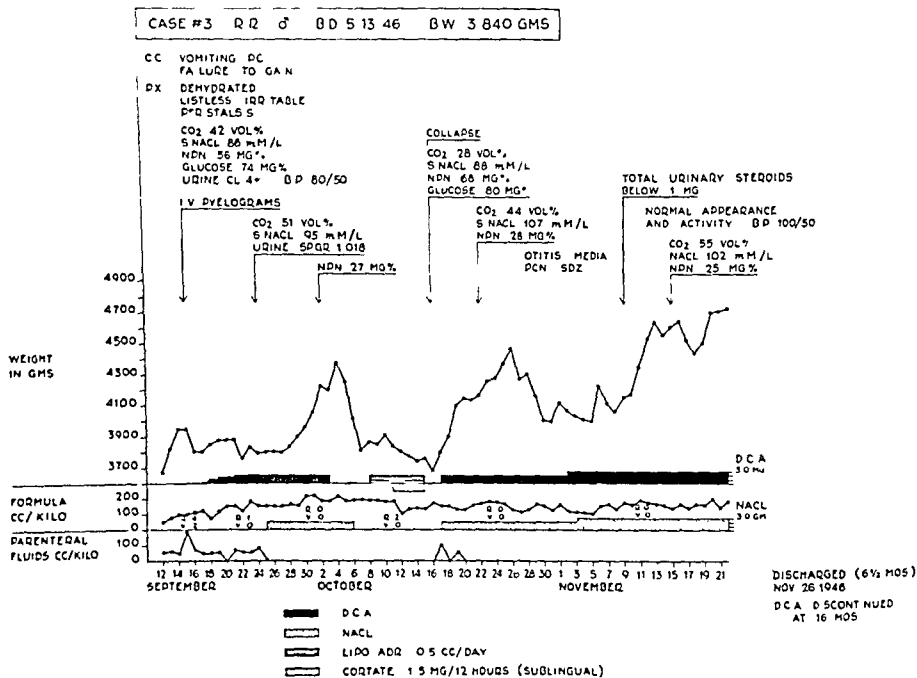


Fig 3—Graphic record, Case 3

CASE 3.—R. R., a full-term, white male infant, was admitted to St. Louis Children's Hospital at 4 months of age. He was apparently normal at birth, but shortly thereafter he began to regurgitate, and occasionally there was projectile vomiting. He remained in a hospital in Memphis, Tenn., for many weeks, but in spite of adequate medical and nursing care there was little improvement. He was alert but emaciated and dehydrated. There was no evidence of infection. The serum sodium chloride and carbon-dioxide combining power were moderately lowered, the nonprotein nitrogen elevated, and the serum glucose normal. The urine contained chlorides in abundance during periods of regurgitation and dehydration. With the usual parenteral fluid therapy there was rapid improvement, but when this treatment was discontinued regurgitation and weight loss resulted. Immediately following the in-

stitution of D.C.A. therapy there was a marked improvement in the general well-being and less tendency to regurgitation; however, there was no appreciable weight gain until table salt was added to the formula. The combination of adrenal steroid and salt resulted in a prompt and rapid disappearance of dehydration and the return of the blood chemistry to normal. The discontinuance of D.C.A. and salt resulted in an immediate loss of weight, regurgitation, and return of the blood chemistry to that seen on admission. A trial on Lipo-Adrenal Cortex and sublingual D.C.A. gave only partial relief. There was no evidence of hypoglycemia. Although many attempts were made to discontinue the D.C.A. it was impossible to do so until the sixteenth month of age. Since this time he has remained in good health and has had no extra salt. Urinary steroids were excreted in imperceptible amounts. The mental and physical growth have continued to be normal.

TABLE III. FOLLOW-UP OF CASE 3

DATE	AGE (MO.)	D.C.A. (MG.)	NaCl. (GM.)	WEIGHT (GM.)	REMARKS
1946					
11/26	6	3.0 daily	3.0	4,750	Discharged from hosp. Condition good.
12/8		3.0 daily	2.0	6,030	Phys. exam. neg. Good appetite. No vomiting. Normal activity. B.P. 104/60. No edema.
1947					
1/3	8	2.5 daily	2.0	7,410	Phys exam. neg.
1/12		1.5 daily	2.0	7,860	Phys. exam.: Ht. 68 cm. B.P. 106/70. No edema. Normal baby. Advice: Gradually reduce D.C.A.
2/1	9	0.5 every other day	2.0	8,400	Phys. exam. neg. B.P. 110/70. Advice: Discontinue D.C.A.
3/3	10	None	2.0		Report—off D.C.A. 1 mo. Doing well.
4/1	11	None	2.0		Report—anorexia, constipation, irritable, vomits occasionally. Advice: 2.0 mg. D.C.A. daily.
4/28		2.0 daily	2.0	8,500	Phys. exam. neg. Ht. 71.5 cm. B.P. 108/68. No edema. Advice gradually reduce D.C.A.
5/3	12	2.0 daily	2.0	9,300	Report—walking with help. Teeth 3./2. Normal activity. Advice: Reduce D.C.A.
7/11	14	1.0 every other day	2.0	10,300	Phys. exam. neg. B.P. 100/56. No edema. Walking 1 mo.
9/22	16	1.0 every three days	2.0	11,400	Phys. exam. neg. B.P. 90/60. Advice: Discontinue D.C.A. and extra salt. Normal since.
1948 1/22	20	None	None	12,480	Report—off steroid and extra salt 4 mo. Has remained well.

DETAILED CASE REPORT

R. R. was born May 13, 1946, and admitted to St. Louis Children's Hospital, Sept. 11, 1946. He was a first child, delivery was normal, cry and respiration were spontaneous, and the birth weight was 3,840 Gm. Almost from birth he was little interested in food and frequently vomited immediately after taking the bottle. The baby left the hospital at 7

days of age, weighing 3,600 Gm. and doing fairly well. At home the vomiting became more severe, at times projectile, and occasionally contained bile. The vomiting occurred immediately after feeding.

The patient was placed on various schedules and eight different formulas, without improvement. The stools were normal. Prolonged hospitalization was necessary in Memphis, and daily parenteral fluids were required. A gastrointestinal series revealed slow emptying time of the stomach. Atropine, thyroid, and thick feedings were tried without benefit. The child was discharged from the hospital at 2 months of age, 210 Gm. below birth weight. After a couple of days at home the vomiting returned and he was readmitted to the hospital. Because of persistent vomiting and pronounced tendency to dehydration, he was brought to St. Louis for further study.

On admission the child was alert, but dehydrated, weak, listless; the skin had a dirty gray color. The genitals were normal. No evidence of infection was found. The urine was alkaline, clear, and contained small amounts of albumin which rapidly cleared. Tuberculin and Kline tests were negative. The carbon-dioxide combining power was 42 volumes per cent, serum sodium chloride 86 mM per liter, nonprotein nitrogen 56.6 mg. per cent, and total proteins 5.88 Gm. He was given 10 per cent glucose in equal parts lactate Ringer's solution subcutaneously. Twenty-four hours later he was in a better state of hydration, seemed much improved, took formula well, and quit vomiting. Three days later, despite a good intake of formula and the giving of subcutaneous fluids, he again became dehydrated. The urine volume was large and had a specific gravity of 1.009, and the chloride test was strongly positive. On September 16 intravenous pyelograms were done, and the dye was seen in the bladder within thirty minutes. In addition to an approximate 100 c.c. of formula per kilogram per day, he required from 60 to 180 c.c. of parenteral fluids per kilogram per day to maintain hydration. Polyuria was mainly responsible for the failure to gain. On September 17, 0.5 mg. D.C.A. without added salt was begun. This was gradually increased to 2.0 mg. of D.C.A. by September 21. During this period there was a gradual increase in food intake, less tendency to regurgitate, and less need for parenteral fluids. (See Fig 3.) He still required about 50 c.c. of parenteral fluids in addition to approximately 150 c.c. of formula per kilogram per twenty-four hours to maintain hydration.

By September 24 the carbon-dioxide combining power was 51 volumes per cent, and the serum sodium chloride 95 mM per liter. The urine volume had decreased from an obvious polyuria to approximately 300 c.c. per day, and the specific gravity rose to 1.018. The blood pressure was 70/40. On September 25, 2.0 Gm. sodium chloride were added to the total twenty-four hour formula. By the time both the salt and D.C.A. were discontinued on October 4, the weight had increased from 3,800 Gm., to 4,380 Gm., without the appearance of edema. With the rapid increase in blood volume there was a corresponding fall in the hemoglobin and during this period the child was given two blood transfusions. On October 2, the serum sodium chloride was 110 mM per liter, nonprotein nitrogen 27 mg. per cent. Immediately after discontinuing both the salt and D.C.A. on October 4, there was a precipitous weight loss of 560 Gm. in three days. This was followed by a gradual reduction in the appetite but no regurgitation. On October 7, the carbon-dioxide combining power had dropped to 45 volumes per cent, the nonprotein nitrogen had risen to 50 mg. per cent, and the serum sodium chloride was 86 mM per liter, the serum glucose 81 mg. per cent, and total protein 7.7 Gm. From October 8 to October 16, Lipo-Adrenal extract in the amount of 0.5 c.c. was given intramuscularly daily, and on October 11, in addition, 1.5 mg. Cortate sublingually three times daily. Although the patient looked well during this period and did not require daily parenteral fluids, there was a gradual weight loss of 300 Gm. On October 17 the patient was found in a state of collapse, gray, and semiconscious. Emergency therapy consisted of 5.0 c.c. Adrenal Cortex Extract in 5 per cent glucose in normal saline, intravenously, 20 c.c. per kilogram. This effected an immediate beneficial response. During the period of impending collapse, the carbon-dioxide combining power was 28 volumes per cent, serum true glucose 84 mg. per cent, nonprotein nitrogen 68 mg. per cent, and the serum sodium chloride 88 mM per liter. On October 18, 2.0 Gm. salt and 2.0 mg. D.C.A. intra-

muscularly were resumed. There was an immediate improvement. The following day the carbon-dioxide combining power was 52 volumes per cent, nonprotein nitrogen 50 mg. per cent, serum sodium chloride 91 mM per liter. The weight gradually rose from 3,650 Gm. on October 17 to 4,450 Gm. on October 27, a gain of 800 Gm. in ten days. There was no evidence of edema. During the period of rapid gain the hemoglobin dropped from 12.0 to 8.5 Gm. From October 17 for a period of one week there was a gradual weight loss, despite giving the same amount of salt and D.C.A. (see Fig. 3). It was necessary to increase the salt to 3.0 Gm. and the D.C.A. to 3.0 mg. daily before there was a continuous satisfactory weight gain. On November 15, while on this dosage, the carbon-dioxide combining power was 55 volumes per cent, nonprotein nitrogen 25 mg. per cent, serum sodium chloride 102 mM per liter. There was no evidence of edema; blood pressure was 100/60. The patient was discharged November 22, at 6 months of age, weighing 4,750 Gm, taking 3.0 Gm. of salt and 3.0 mg. D.C.A. daily. He was again seen at 7 months of age. The weight was 6,030 Gm., length 63 cm., blood pressure 104/60, hemoglobin 12.5 Gm. The child was sitting, had good appetite, was not vomiting, and in every respect seemed normal. On Jan. 3, 1947, the weight was 7,410 Gm. D.C.A. was gradually reduced to 2.0 mg. and salt to 2.0 Gm. The height was 70 cm., blood pressure 104/70. On February 1 at 8½ months, it was possible to decrease the D.C.A. to 0.5 mg. every other day. The weight was 8,400 Gm., height 72 cm., blood pressure 108/70. There was no evidence of edema. The mother was advised to discontinue D.C.A., but continue 2.0 Gm. of salt. He did well for three weeks, then gradually began to refuse food, became irritable, constipated, lost weight, and then began to vomit. Two milligrams D.C.A. and 2.0 Gm. salt were resumed. At 11 months of age, the weight was 8,880 Gm., length 73 cm., blood pressure 110/70. He became somewhat of a feeding problem due to the natural desire on the part of the mother to encourage him to eat. At 14 months of age, the weight was 11,460 Gm., height 77.5 cm. He had been walking one month and was a normal, happy baby. The D.C.A. had been gradually reduced to 1.0 mg. every other day, and he was still taking 2.0 Gm. of salt per day. The D.C.A. was then reduced to 1.0 mg. every three days and by Sept. 24, 1947, to 0.5 mg. every three days. By October 5, it was possible to eliminate the injections. No extra salt has been given since this time. The child has remained perfectly normal. The urine was examined by Dr. Willard Allen for 17-ketosteroids, and none was found.

CASE 4.—J. B. was a normal, full-term white male infant, who did well for the first two weeks of life. There was an insignificant amount of spitting-up the first couple of weeks, but following this he began to regurgitate frequently and vomit occasionally. Two days before admission to St. Louis Children's Hospital, at 5 weeks of age, almost all of the feedings were vomited immediately after taking. He was found lethargic and dehydrated. Intestinal patterns were seen, and it was thought he was in a state of alkalosis. A tentative diagnosis of pylorospasm or pyloric stenosis was made by the admitting physician. The blood chemistry, however, revealed the carbon-dioxide combining power to be moderately low, serum sodium chloride markedly low, and nonprotein nitrogen elevated; the serum sodium was definitely low and serum potassium elevated. Despite the presence of dehydration, there were large amounts of chlorides in the urine. After a short period of observation in the hospital, which resulted in no appreciable weight gain despite daily parenteral fluids, intramuscular D.C.A. was begun. There was a slow but steady weight gain and no further need for fluid therapy. It was not until extra salt was added to the formula that the expected rapid weight gain and increased formula intake was noted. Following this therapy the blood chemistry returned to normal. The child's activity and appearance became normal. After D.C.A. was

discontinued the weight remained stationary, and after the salt was removed from the formula there was a rapid weight loss and appearance of a dirty gray color of the skin, decreased appetite, irritability, and resumption of the tendency to regurgitate. One week following discontinuance of adrenal and salt therapy the child was found in a state of collapse. Adrenal Cortex Extract was given for a short time without extra salt, and although the patient did not gain weight, he did not lose or become dehydrated and looked fairly well. The appetite remained poor until salt was added to the formula; then there was an abrupt weight gain and increase in appetite. During the period of collapse, the blood chemistry was similar to that seen on admission. Following the ad-

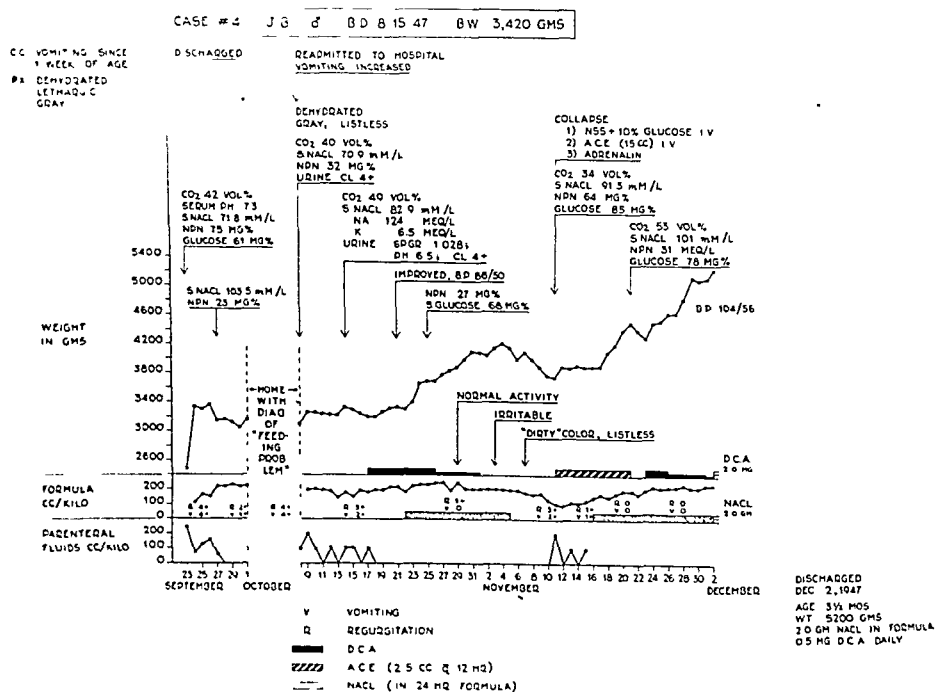


FIG. 4.—Graphic record, Case 4.

ministration of salt and whole gland, the blood chemistry rapidly returned to normal. A glucose tolerance test was normal, and there was no evidence of hypoglycemia. The patient was regulated on intramuscular D.C.A. and salt. The blood pressure remained normal, and there was no edema at any time during the course of hormone therapy. The steroid was gradually reduced and finally discontinued at 5½ months of age. The child has remained well and looks and acts normal in every respect for an infant of his age. Dr. Willard Allen's laboratory reports small amounts of steroids in the urine. This finding is of questionable significance. The genital development has remained normal for age.

TABLE IV. FOLLOW-UP OF CASE 4

DATE	AGE (MO.)	D.C.A. (MG.)	NaCl. (GM.)	WEIGHT (GM.)	REMARKS
1947 12/3	3½	0.5 daily	2.0	5,300	Discharged from hospital. Condition good.
1948 1/8		0.5 daily	2.0	7,500	Phys. exam.: B.P. 118/70. No edema. Normal skin. Ht. 63 cm. Normal activity. R 0.5 mg. D.C.A. every other day.
1/15	5	0.5 every other day	2.0	7,620	Phys. exam. neg. R: 0.5 mg. every 3 days.
1/29	5½	0.5 every 3 days	2.0	8,280	Phys. exam.: B.P. 110/60. No edema. Normal activity. R: Discontinue D.C.A.
2/10	6	None	2.0	9,100	Phys. exam: Normal activity. Ht. 66 cm. B.P. 100/60. Firm tissue.
2/14		1.0 daily	2.0	8,500	Refusing food 2 days, irritable, vomited today. Phys. exam.: Dirty gray color, no infection. B.P. 80/50. CO_2 47 vol. %. N.P.N. 40 mg. %. S. NaCl 98.4 mM/L. Advice: Resume D.C.A. and NaCl.
2/17		1.0 daily	2.0	9,270	Phys. exam. neg. B.P. 108/50. No edema. Advice: 0.5 mg. D.C.A. daily.
2/23	6½	0.5 daily	2.0		Report—doing well. Advice: 0.5 mg. D.C.A. every other day and gradually decrease.
2/29		0.25 every other day	1.0	9,400	Report—doing well. Advice: 0.25 mg. D.C.A. every other day.
3/6	7	None	1.0	9,430	Phys. exam.: Excellent health. B.P. 90/50. No edema. Advice: Discontinue or NaCl. Has remained well.

DETAILED CASE REPORT

J. B. was born on Aug. 15, 1947. Delivery was normal; the weight was 3,420 Gm. The first two weeks at home he did quite well. He did not take more than 75 c.c. of formula at any one time. At 2 weeks of age he weighed 2,510 Gm. At this time he began to regurgitate and occasionally there was projectile vomiting. The vomitus did not contain bile, and the stools were normal. He was admitted to St. Louis Children's Hospital at 5 weeks of age, because of vomiting and weight loss.

The admission physical examination revealed a dehydrated, lethargic infant, who aroused easily when disturbed. The genitals were normal. There were intestinal patterns but no definite gastric waves. The impression of the admitting physician was that this was a pyloric stenosis or pylorospasm, and he thought the child might be in a state of mild alkalosis. The color was gray, and an oxygen tent was required. There was no evidence of infection or diarrhea. The serum carbon-dioxide combining power was 42.5 volumes per cent and pH of the blood 7.3. The centrifuged urine contained 10 white blood cells per low power field, no casts, heavy trace of albumin, and a pH of 5.5. Hemoglobin was 17.1 Gm., white blood count 28,950, and the differential was: stabs 9, segmentals 41; lymphocytes 48, monocytes 2. Intravenous and subcutaneous fluids were administered in the amounts of 150 c.c. per kilo for the next twenty-four hours, and smaller amounts were required about every other day for the next nine days. The formula intake during this period averaged around 200 c.c. per kilogram per day, and the patient vomited from one to four times daily. On September 25, following hydration, the hemoglobin dropped to 9.0 Gm. and the white

blood count to 7,000, with a normal differential. The trace of albumin in the urine disappeared. Intravenous pyelograms were reported negative. The child was given a couple of blood transfusions and sent home with a diagnosis of "feeding problem." He was readmitted a few days later, dehydrated, gray, and listless. The vomiting had increased. The carbon dioxide combining power was 40 volumes per cent, serum sodium chloride 70.9 mM per liter, and the nonprotein nitrogen 32 mg. per cent. During the period of dehydration the urine was excessive and contained large amounts of chlorides. Urine specimens showed the pH below 7.0 and specific gravity ranging from 1.008 to 1.028. On October 14, six days following readmission and after parenteral fluid therapy, the carbon-dioxide combining power of the serum was 49 volumes per cent, the serum sodium chloride 82.9 mM per liter, serum sodium 124 meq. per liter, and serum potassium 6.5 meq. per liter. On October 17, at 2 months of age, desoxycorticosterone acetate was begun, 2.0 mg. daily. Before therapy the weight was 3,200 Gm., and six days later it had risen only to 3,300 Gm. However parenteral fluids were no longer required, and the baby showed definite improvement. On October 22, 2.0 Gm. of sodium chloride were added to the total twenty-four hours' formula. There was a gain of 800 Gm. during the next nine days. During this period the patient's appetite improved, the formula intake averaging around 200 to 250 c.c. per kilo gram per day. The blood chemistry returned to normal and the vomiting ceased. There was no evidence of edema.

On November 1, D.C.A. was discontinued but the 2.0 Gm. of salt maintained. The weight gain stopped, but otherwise the child looked all right. On November 5, four days later, the salt was removed from the formula. Six days later the patient was found in a state of collapse, was gray, very lethargic, and would respond only to painful stimuli. Regurgitation reappeared, and there was a loss of 500 Gm. The serum carbon-dioxide combining power was 31 volumes per cent, serum sodium chloride 91 mM per liter, nonprotein nitrogen 64 mg. per cent. Five cubic centimeters of Adrenal Cortical Extract and 5 per cent glucose in normal saline were given intravenously in amounts of 20 c.c. per kilo. Immediate improvement followed, but a short time later the same lethargy was again noticed. The blood sugar was 100 mg. After the administration of adrenalin, two minims every hour for the next few hours, the child showed sustained improvement.

Following recovery from collapse, Adrenal Cortex Extract was begun, 2.5 c.c. every twelve hours subcutaneously without the addition of extra salt. For the next five days the weight remained stationary, the appetite gradually increased, and the patient looked much better. The appetite did not return to normal, however, nor was there an appreciable increase in weight until the addition of 2.0 Gm. of salt to the formula. During the next five days while on Adrenal Cortex Extract and added salt, the weight increased from 3,900 Gm. to 4,500 Gm., and there was a remarkable improvement in the general appearance and activity of the baby. The color became pink, his playful and happy disposition returned, and the intake of formula again averaged 200 c.c. per kilogram per day. During A.C.E. and salt therapy the carbon-dioxide combining power was 53 volumes per cent, serum sodium chloride 101 mM per liter, nonprotein nitrogen 31 mg. per cent, glucose 78 mg. per cent. Specific gravity of the urine was 1.018, pH 5.5, and average amounts of chlorides were present in the urine. From November 21 to November 23 the patient did not receive the adrenal extract, and by mistake the salt was omitted from the formula. The weight dropped from 4,500 Gm. to 4,300 Gm. in this brief period, though no vomiting occurred and there was the usual intake of formula. On November 23 salt was once more added, and the patient was started on 1.0 mg. D.C.A. daily intramuscularly. From this time on there was a rapid weight gain, and six days later the weight had increased to 5,180 Gm. A glucose tolerance test revealed: fasting sugar 80 mg. per cent; one half hour after ingestion of glucose, 172 mg. per cent; one hour, 104 mg. per cent; two hours, 96 mg. per cent; three hours, 78 mg. per cent; four hours, 68 mg. per cent. Three minims of adrenalin were given at the end of the test and one half hour later the blood sugar was 133 mg. per cent. On November 27 the hemoglobin was 10.4 Gm.; R.B.C. 4 million; W.B.C. 13,150; eosinophiles 2, stab 3, segmental 28, lymphocytes 64, monocytes 3. A number of individual determinations of fasting blood sugars were made over a period of a couple of weeks. The

lowest was 68 mg. per cent and the highest, 96 mg. per cent. During the time the salt was left out of the formula, a twenty-four hour urine specimen was collected, and it was found that the urine contained 5.0 Gm. of sodium chloride per liter. While on D.C.A. and salt therapy the carbon-dioxide combining power was 49 volumes per cent, nonprotein nitrogen 24 mg. per cent, serum sodium chloride 105 mM per liter. On December 2 the weight was over 5,300 Gm., and the dose of D.C.A. was decreased to 0.5 mg. daily. The mother was taught to give intramuscular injections of D.C.A., and the child was discharged on December 3 at 3½ months of age, in excellent condition. His diet during the hospital stay consisted of the usual proportions of Formulac, water, and Karo, in addition to large amounts of multiple vitamins, including ascorbic acid.

Dr. Willard Allen's laboratory reported 6.1 mg. of sodium pregnanediol glycuronide and 2.2 mg. of 17-ketosteroids in the twenty-four hour urine sample.

By Jan. 8, 1948, at 5 months of age, the weight had increased to 7,500 Gm., the height to 63 cm. The blood pressure was 118/70, taken while crying. There was no edema. The baby appeared normal in every respect. The tissue did not feel thick and soapy as in Case 1. The D.C.A. was decreased to 0.5 mg. every other day. By January 29 he was still doing well. The blood pressure was 100/60. The weight was 8,250 Gm. D.C.A. and extra salt were discontinued. On February 10 the weight was 9,100 Gm. The blood pressure was 98/60; color and activity were normal.

Two days later the child began to refuse milk but took solid foods well; however, the following day he appeared nauseated, became very irritable, and vomited. On February 14, sixteen days following the discontinuance of hormone therapy, the weight was 8,500 Gm. He was quite irritable and had the characteristic dirty gray color. There was no evidence of infection. The white blood count was 17,500, with stab 4, segmentals 31, lymphocytes 56, monocytes 9; the urine was loaded with chlorides. The carbon-dioxide combining power was 47 volumes per cent, nonprotein nitrogen 40 mg. per cent, and serum sodium chloride, 98.4 mM per liter. Because of the persistent vomiting, normal saline solution plus 5.0 c.c. of A.C.E. was given intravenously. The mother was instructed to put the 2.0 Gm. of salt in the formula and give 1.0 mg. D.C.A. daily. There was an immediate and satisfactory response.

The D.C.A. and salt were gradually reduced to 0.25 mg. every three days and eventually discontinued three weeks later. The child has remained well.

CASE 5.—J. T., a full-term, white male infant, was apparently normal at birth. During the first few weeks of life regurgitation was frequent, and at times there was projectile vomiting. The referring pediatrician stated that gastric waves were visible, and a barium meal showed delayed emptying time of the stomach. Parenteral fluids were frequently required to maintain hydration. At 5 weeks of age, an operation for pyloric stenosis was performed without relief of symptoms. No pyloric tumor was found. He was admitted to St. Louis Children's Hospital at 2½ months of age. He was poorly nourished, gray, dehydrated, and irritable. There was no evidence of infection, other than a small stitch abscess of the abdominal wall. The carbon-dioxide combining power of the serum was low, the serum sodium chloride moderately reduced, and the nonprotein nitrogen elevated. The stools were normal. Intestinal patterns were seen but no definite gastric waves noted. During five weeks of observation, the weight increased only 150 Gm. The child frequently regurgitated and occasionally required parenteral fluids to maintain hydration, despite an adequate caloric and fluid intake. Subsequent blood chemistry determinations also revealed a moderately low carbon-dioxide combining power, slight reduction of serum sodium chloride, and elevation of the nonprotein nitrogen. It was only after beginning D.C.A. therapy that

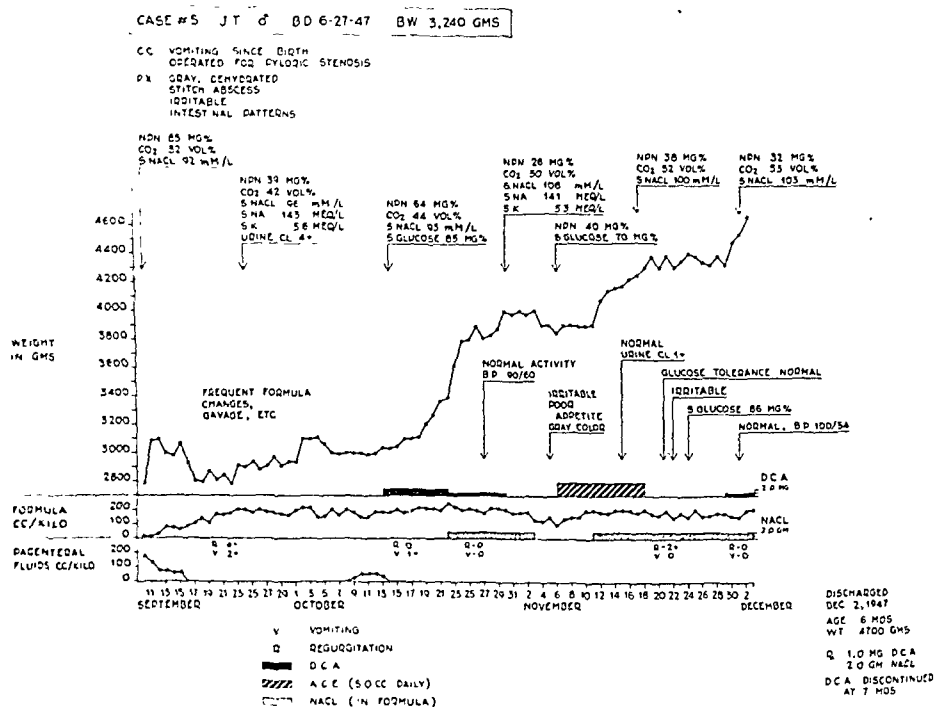


FIG. 5.—Graphic record, Case 5.

TABLE V. FOLLOW-UP OF CASE 5

DATE	AGE (MO.)	D.C.A. (MG.)	NaCl. (GM.)	WEIGHT (GM.)	REMARKS
1947					
12/2	5	1.0 daily	2.0	4,700	Discharged from hospital. Condition good.
12/30	6	1.0 daily	2.0	6,540	Phys. exam.: Normal activity. B.P. 92/50. No edema. Ht. 60 cm. (father, 162 cm., mother 147.5 cm.). Advice: 0.5 mg. D.C.A. daily.
1948					
1/13		0.5 daily	2.0	6,720	Phys. exam. neg. R: 0.5 mg. D.C.A. every other day.
2/3	7	0.5 every other day	1.5	7,560	Phys. exam.: Normal activity. Ht. 62 cm. B.P. 130/70 (crying). Advice: Discontinue D.C.A.
2/14		None	1.0	7,680	Report—Not gaining as rapidly; otherwise in excellent health.
2/24	8	None	None	7,750	Phys. exam.: Sitting Ht. 63 cm. B.P. 90/50. Rt. O.M. R: S.D.Z. No D.C.A. or NaCl. Has remained well.

the patient showed any real improvement. D.C.A. without salt resulted in a slow, steady weight gain, better color, less tendency to regurgitation. When salt was added to the formula, there was a more rapid gain in weight and a still further improvement in the general welfare of the patient, and the blood chemistry returned to normal. When the dose of D.C.A. was lowered there was an associated decrease in the amount of weight gain, and when the steroid was discontinued the weight remained stationary and baby became irritable. Adrenal cortex extract without salt did not produce desired results, but when the salt was added there was a response similar to that seen with D.C.A. Examination of the urine revealed an excess amount of sodium chloride and slight increase in 17-ketosteroids. A glucose tolerance test and frequent individual determinations of the fasting blood sugar showed no abnormality in the carbohydrate metabolism. The patient was discharged after eleven weeks of hospitalization in excellent health. The D.C.A. and salt were gradually decreased and eventually eliminated two months later. The child has remained well and has shown no abnormal genital development.

DETAILED CASE REPORT

J. T. was born on June 27, 1947. Delivery was normal; the birth weight was 3,220 Gm. He was a first child; the family history was essentially negative. When he was a few days of age he began to regurgitate immediately after feedings. In every other respect he appeared perfectly normal. The baby was hospitalized by a well known pediatrician in Springfield, Ill. He was given parenteral fluids, blood transfusions, and observed on different formulas. Because of the occasional appearance of gastric waves, a delayed emptying time of the stomach, and failure to improve after prolonged hospital stay, he was operated on for pyloric stenosis at the age of 5 weeks. No tumor was found. Since there was no improvement in the tendency to regurgitation, he was admitted to St. Louis Children's Hospital on Sept 10, 1947, at 2½ months of age. At this time he was found to be dehydrated and poorly nourished, but fairly alert and hungry. Intestinal patterns were well outlined over the entire abdomen. The heart was small but normal. Two small abscesses were found in the suture lines near the operative wound. The temperature was 38.6° C. At this time it was thought that the patient had a high intestinal obstruction and a possible peritonitis. The blood culture was sterile. Hemoglobin was 13.6 Gm.; the white blood count was 21,350, eosinophiles 2, stab 6, segmentals 28, lymphocytes 63, monocytes 1. The serum carbon dioxide combining power was 32 volumes per cent. Serum sodium chloride was 92 mM per liter, nonprotein nitrogen 86.5 mg per cent. The usual amounts of molar lactate, intravenous glucose, Ringer's, and blood transfusions were given. Visualization of the gastrointestinal tract showed some delay in emptying time of the stomach but no definite obstruction. No genuine peristaltic waves were seen. For the next five days, daily parenteral fluid therapy was required to maintain hydration. Following hydration the carbon dioxide combining power was 56 volumes per cent, and the nonprotein nitrogen 38 mg per cent. The child looked much better, there was little regurgitation, and the food intake gradually increased. On September 20 regurgitation reappeared, but not in sufficient degree to be alarming. The weight remained stationary despite an intake of formula around 200 c.c. per kilogram per day (see Fig 5). The weight on admission was 2,800 Gm., and one month after hospitalization the weight was 2,900 Gm. Regurgitation, although frequent, was not sufficient to account for the failure to gain. The nurse commented that the diapers were always saturated, and it was thought that an abnormal amount of urine was being excreted. Occasionally the pH of the urine was above 7.0. On October 12, the weight was 2,940 Gm., the patient was gray, listless, and slightly dehydrated. A urine specimen at this time showed a specific gravity of 1.019 and pH 5.5, and contained an abundance of chlorides. It was again necessary to administer parenteral fluid therapy. On October 10, the carbon dioxide

ombining power was 44 volumes per cent, serum sodium chloride 92 mM per liter, nonprotein nitrogen 64 mg. per cent, and blood sugar 55 mg. per cent. For the next eight days 2.0 mg. D.C.A. without added salt was the only therapy. The weight gradually increased from 3,000 Gm. to 3,400 Gm. over this period. There was definite improvement in the baby's general condition and less regurgitation. On October 17, four days after therapy, the serum sodium was 113 meq. per liter and potassium 5.6 meq. per liter. On October 22, 2.0 Gm. of salt were added to the formula. During the next two days the weight jumped 400 Gm., without the appearance of edema and with obvious improvement of the patient. D.C.A. was then reduced to 1.0 mg., and this was followed by a slow weight gain to 4,000 Gm. by October 30. During this period there was no evidence of edema, blood pressure was 90/60, the heart was normal size, and the urine contained smaller amounts of chlorides. On October 27 the twenty four hour urine sample contained 11.2 mg. of sodium pregnanediol glycuronide and 1.5 mg. of 17 ketosteroids. The significance of this finding is still a matter of conjecture. On October 30, the carbon dioxide combining power was 50 volumes per cent, serum sodium chloride 106 mM per liter, nonprotein nitrogen 26 mg. per cent. At this time D.C.A. was stopped but the salt continued. For the next five days the weight remained stationary, even though the formula intake remained around 200 c.c. per kilogram per day and there was no tendency to regurgitation. After the fifth day of omission of D.C.A., the child became irritable, the formula intake decreased to 120 c.c. per kilogram, the color became slightly gray, and regurgitation and constipation reappeared. From November 4 to November 6 the weight decreased 200 Gm. On November 6, Adrenal Cortex Extract, 2.5 c.c., was given subcutaneously every twelve hours and the salt discontinued. For the following six days there was no further weight loss, and a gradual improvement in the appearance of the baby, increased appetite, and decreased regurgitation were observed. On November 6, when the baby was slightly gray and irritable, the blood sugar was 70 mg. per cent and the non protein nitrogen 40 mg. per cent. On November 11, after five days of A.C.E. therapy without salt, the carbon-dioxide combining power was 55.8 volumes per cent, total serum sodium chloride 92 mM per liter, nonprotein nitrogen 44 mg. per cent, blood sugar 61 mg. per cent. On this date, November 11, 2.0 Gm. of salt were again added to the formula and Adrenal Cortex Extract continued in the same dosage. There was an immediate rapid weight gain from 3,800 Gm. to 4,200 Gm. in five days. During this period the child appeared normal in every respect. On November 16 the A.C.E. was stopped; the carbon-dioxide combining power was 52 volumes per cent, total sodium chloride 100 mM per liter, nonprotein nitrogen 38 mg. per cent. For the next five days the patient was kept on 2.0 Gm. of salt, but no hormone was given. The weight remained stationary for a day or two and then gradually decreased. On November 22, after the adrenal cortex extract had been discontinued for five days, a glucose tolerance test was done. Fasting sugar was 84 mg. per cent; one half hour after ingestion of glucose, 127 mg. per cent; one hour, 107 mg. per cent; 2 hours, 70 mg. per cent; three hours, 89 mg. per cent; four hours, 73 mg. per cent; five hours, 76 mg. per cent. Three minims of adrenalin were given at the end of the test, and thirty minutes later the blood sugar had risen to 104 mg. per cent. On November 23, extra salt was omitted from the formula and a twenty four hour urine sample was collected. Five grams of sodium chloride per kilo of urine were excreted. On November 24, 2.0 Gm. of salt were again added to the formula. There was no gain in weight, the appetite remained only fair, and by November 29 it was thought necessary to resume injections of D.C.A. The child was given 1.0 mg. D.C.A. daily, in addition to the salt. This was followed by an abrupt weight gain from 4,300 Gm. to 4,700 Gm. in four days without the appearance of edema. The appetite increased appreciably during this time. On December 1, the carbon-dioxide combining power was 53 volumes per cent, serum sodium chloride 103 mM per liter, nonprotein nitrogen 35 mg. per cent. The urine pH was 6.5, the specific gravity 1.030. Tuberculin and Wassermann tests were negative. By December 2 it was possible to reduce the D.C.A. to 1.0 mg. daily. The mother was taught to give the injections. The patient was discharged on December 2 at 5 months of age, weighing 4,700 Gm.

He was seen again on December 30. The height was 60 cm., weight 6,540 Gm., blood pressure 90/50; there was no edema, and color and activity were normal. (The father is 162.5 cm and the mother, 147.5 cm. in height.) The D.C.A. was reduced to 0.5 mg. daily

and salt to 1/3 teaspoonful. The child continued to do well, and by Jan. 13, 1948, the steroid could be reduced to 0.5 mg. every other day. On February 2, at 7 months of age, the hormone was discontinued, and one week later the extra salt was removed from the formula. He has remained well.

DISCUSSION AND SUMMARY

From the study of Addison's disease, Cushing's syndrome, and Simmond's disease, and investigations of the metabolic changes associated with the urinary excretion of adrenal steroids during pregnancy,¹² evidence is rapidly accumulating that the various functions of the adrenal glands may vary independently of one another. It is therefore not surprising that we have found clinical evidence of a fractional disturbance of the adrenals during the period of physiologic low activity.

The patients presented here required administration of desoxycorticosterone acetate and salt for long periods to sustain life.

None of these patients, nor their relatives, showed signs of endocrine disturbances. The blood chemistry findings of low carbon-dioxide combining power, elevated nonprotein nitrogen, and moderately low serum sodium chloride during periods of hemoconcentration were present in all cases. A moderately low serum sodium and elevated potassium were present in three of the four patients in whom these determinations were made. These findings, together with the patients' clinical course before, during, and after hormone therapy, are presented as evidence suggesting a temporary absence or physiologic low supply of the desoxycorticosterone factor of the adrenal cortex.

That the administration of salt and D.C.A. is adequate replacement therapy is suggested by (1) failure to demonstrate hypoglycemia, (2) normal glucose tolerance tests, (3) no evidence of low adrenal function, except the defect in water and electrolyte metabolism, and (4) the return to normal activity and appearance and the subsequent healthy development of the infants during therapy.

Evidence that there is no anatomic abnormality of the adrenal glands may be found in the following: negative family history, absence of macrogenitosomia and skin pigmentation, the finding of imperceptible amounts of steroids in the urine in the majority of cases, and the all-important fact that D.C.A. and salt can eventually be discontinued.

The patients presented offer certain characteristics in common. All are male children and were considered to be perfectly normal at birth (I have seen two female children with this syndrome). Symptoms referable to the upper gastrointestinal tract developed during the neonatal period. Anorexia, regurgitation, and vomiting were present to some degree in all patients. Vomiting was at times projectile in two patients. The vomitus rarely contained bile. Quite frequently, intestinal patterns and occasionally gastric waves developed suggesting the diagnosis of a high partial obstruction. Before two of the infants were admitted to our hospital they were mistakenly operated upon for pyloric stenosis. Although an infrequent loose stool was recorded, no diarrhea was noted at any time. After a few days of these symptoms of "feeding problem," characterized by periods of improvement alternating with periods of failure to gain

and excessive weight loss out of proportion to the amount of food regurgitated, there gradually came a time when the administration of fluids became essential to maintain hydration. Before hydration the skin was a dirty gray in color, and the children were listless and fretful. During the periods of hydration all the infants had good muscle tone, fairly good appetites, and showed definite improvement in general well-being and color of the skin. Following the administration of D.C.A. or A.C.E. and addition of 2.0 to 3.0 Gm. of salt to the formula, they rapidly resumed their normal healthy color, appetites continued to improve, abnormal regurgitation and vomiting disappeared, the weight gain was rapid, and the blood chemistry gradually returned to, and remained within, the normal range, without need of parenteral fluids.

During the periods of vomiting, weight loss, and dehydration, excessive amounts of urine of low specific gravity were excreted, and qualitative determinations revealed large amounts of chlorides. During the period of weight gain following administration of D.C.A., with or without added salt, the urinary chlorides and volume of urine output diminished.

It has been shown that the adrenal hormones increase the renal tubular reabsorption of sodium, chloride, and water and therefore play an important role in the maintenance of hydration.¹⁴⁻¹⁷

Although the cases are similar in clinical manifestations they differ in other respects. The total steroid content of the urine was examined in all patients. In three there were imperceptible amounts, and in two there was a moderate increase in the 17-ketosteroids and the steroids expressed as sodium pregnandiol glyceruronate (NaP.G.). If frequent determination of the steroid excretion could be made, however, there might be no differences. Dr. Willard Allen and I believe that periodic increases in the urinary steroids may be a normal mechanism on the part of the adrenal tissue to compensate for the deficiency of the desoxycorticosterone factor. There has been no reason to suspect that the temporary deficiency presented here is secondary to encroachment of a hyperplastic androgenic zone on the true cortex, as is likely in the cases associated with macrogenitosomia.

The blood sodium and potassium determinations were normal in Case 5. It is generally agreed that the sodium and potassium of the blood may be perfectly normal in some cases of Addison's disease and in adrenalectomized animals.

The consistent laboratory findings present before therapy are: (1) moderate reduction in the carbon-dioxide combining power of the serum; (2) moderate elevation of the nonprotein nitrogen; (3) normal to low serum sodium chloride in the presence of low blood volume; (4) abundance of chlorides in the urine.

Infants with these findings who present protracted and unexplained symptoms referable to the upper gastrointestinal tract and who require parenteral fluid therapy to maintain hydration, deserve a trial on sodium chloride and desoxycorticosterone acetate.

From my experience with these and other cases it does not appear likely that a specified amount of D.C.A. per kilogram should be given. The dose should be regulated according to the individual need at that particular time.

Case 1 eventually required 5.0 mg. D.C.A. and 3.0 Gm. salt daily, whereas Case 4 was properly regulated on 0.5 mg. D.C.A. and 2.0 Gm. of sodium chloride. In general, however, it can be said that the steroid without added salt gives only temporary and partial relief. Adequate therapy is a combination of salt and D.C.A. or A.C.E. (see Figs. 1-5). Because of the added expense of A.C.E., the more painful injections, and the lack of evidence suggesting that it is superior to the steroid, it becomes a secondary choice for maintenance therapy. In the treatment of shock where immediate response is imperative, the intravenous injection of A.C.E. in normal saline is more efficacious than D.C.A. Theoretically the use of a whole gland preparation over a prolonged period may suppress the secretion of other steroids. The beneficial response obtained from the use of A.C.E. is most likely due to the presence of the desoxycorticosterone fraction.

Through the trial and error method, I have concluded that an adequate dose for most patients during the period of regulation is approximately 2.0 Gm. of sodium chloride and 2.0 mg. of D.C.A. daily. This dosage is maintained until the time when it can safely be decreased and eventually eliminated. Case 1 could not be taken off intramuscular D.C.A. until 18 months of age. At that time, regulation was accomplished with the use of sublingual Cortate. The child was 29 months old before the mother would permit the extra salt and sublingual steroid to be permanently discontinued. Cases 2 and 3 were 13 and 16 months of age respectively before hormone and salt therapy could be discontinued. These patients could not be properly regulated on sublingual Cortate. Cases 4 and 5 were adequately regulated at 3 and 5 months of age, respectively. It was possible to discontinue the salt and steroid in Case 5 approximately two months later. Case 4, 7 months of age, has been without hormone and salt therapy only a few days.

The use of D.C.A. sublingually may be considered after the patient is older and well regulated. It appears that its use before this time is uncertain. The sublingual preparation caused severe irritation of the throat and the tongue in Case 2.

Although these patients most likely represent the severest type of case, it is probable that all degrees of deficiency exist. Some infants may not require D.C.A. therapy for longer than a few days. Case 1 got along well for a few weeks with only the addition of 3.0 Gm. of salt to the formula. It is barely possible that extra salt alone will suffice in some cases.

Signs of overdosage should be constantly kept in mind. During the first few days of therapy there is an immediate and rapid weight gain out of proportion to the caloric intake. This is accompanied by a rapid return of the blood volume to normal and restoration of hydration. Following this phase, the weight gain is slower and nearer the normal average for age. With continued increase of weight at an unprecedented rate, the appearance of edema, or the abnormal elevation of the blood chloride, the adrenal steroid or salt or both should be reduced. I have not seen definite evidence of overdosage in these and other cases.

The symptoms resulting from too early withdrawal of D.C.A. are, in order of frequency: (1) anorexia, regurgitation, or both, (2) irritability, (3) nausea,

(4) vomiting, (5) dirty gray color of the skin, (6) dehydration and shock. This picture may be confused because of the frequency of superimposed symptoms caused by repeated respiratory and other infections to which children of this age group are susceptible.

Differential Diagnosis.—

1. *Feeding Problem:* During the first few days or weeks of life, the mild "self-regulating" type of patient will most likely be considered to have pylorospasm or to be a feeding problem. Most of the patients reported here were considered to be merely feeding problems until prolonged hospitalization was necessary. Cases 2 and 4 were sent home following the first hospitalization with this diagnosis. With the appearance of rapid weight loss and tendency to dehydration, the diagnosis of feeding problem is obviously untenable.

2. *High Partial Intestinal Obstruction:* The intermittent appearance of gastric waves, the presence of intestinal patterns, and slow emptying time of the stomach led to the operation for pyloric stenosis in Cases 1 and 5. Gastric waves or intestinal patterns may be present, but are never persistent. The carbon-dioxide combining power of the serum is normal to low, as contrasted with the common tendency to alkalosis in patients with pyloric stenosis. The excretion of large amounts of chloride in the urine during periods of dehydration is rarely, if ever, seen in uncomplicated cases of pyloric stenosis. It seems that an intimate relationship exists between the motility of the upper gastrointestinal tract and the availability of adequate amounts of the desoxycorticosterone factor or sodium chloride or both. Following regulation on this steroid, the vomiting subsides and the intestinal patterns disappear. When the hormone is prematurely discontinued, there is a return of the signs of partial intestinal obstruction with vomiting in a few and regurgitation in all cases.

3. *Congenital Renal Defects:* Manifestations such as polyuria, acidosis from failure of sodium reabsorption, hypochloridemia, dehydration, azotemia, vomiting, and failure to gain weight are also frequently seen in renal insufficiency on an organic basis. Glomerular nephritis and pyelonephritis are usually easily diagnosed, but, as pointed out by Hartmann,¹⁸ congenital defects without kidney enlargement may be less easily detected because of absence from the urine of formed elements of nephritis and all but traces of protein.

Administration of D.C.A. failed to improve infants with congenital renal defects (unpublished cases).

Thorn¹⁹ presented two cases of renal failure simulating adrenocortical insufficiency and gave this syndrome the name "salt-losing nephritis." These patients were adults who showed typical ante- and post-mortem findings of severe renal insufficiency. No benefit was derived from D.C.A. therapy.

In 1939 Hartmann²⁰ reported on an infant with a peculiar renal defect apparently limited only to failure of HCO_3 reabsorption, leading to severe acidosis, which for months required very large amounts of sodium lactate for prevention. He now feels this child might very well have been the type of infant described in this paper.

The question has been raised: Do infants such as those studied in this paper suffer primarily from adrenal hypofunction or could they possibly rep-

resent an immature type of renal development, perhaps similar to but not identical with that of premature and very young infants, and where D.C.A. in excess of the normal is necessary for more adequate tubular function?

The arguments against this hypothesis are:

A. Premature and full-term infants have poor renal clearances for sodium, chloride, and potassium; however, the premature and young infant may reabsorb more sodium and chloride per cubic centimeter of glomerular filtrate than the older child or adult.²¹⁻²²

B. D.C.A. therapy does not aid in the reabsorption of sodium and chloride in patients with anatomic lesions of the renal tubules.¹⁹

C. Macrogenitosomias associated with adrenocortical insufficiency^{9-11a} are proved cases of congenital abnormalities of the adrenal glands. These patients responded beneficially to the same type of therapy given the infants described in this paper.

D. The increased amounts of urinary steroids in two of the patients point to an intimate association of the adrenal cortex with this syndrome.

Distinguishing the type of infant I have discussed from the child with recognizable primary renal pathologic changes are the following considerations:

The carbon-dioxide combining power of the serum is low but never markedly so. The lowest recorded was 26 volumes per cent, but the average is between 40 and 45 volumes per cent. The mild acidosis most likely results from failure of the renal tubules to reabsorb sodium as in Addison's disease. The elevated nonprotein nitrogen is associated with hemoconcentration and in most cases can promptly be lowered when hydration is established. The serum sodium chloride is normal to reduced, even in the presence of low blood volume. This suggests that a real loss of chloride has taken place out of proportion to the degree of vomiting. The specific gravity of the urine changes from low to values as high as 1.028. Pyelograms that have been done are nonrevealing. The urine is continuously loaded with chlorides, even in the presence of dehydration and vomiting. This is not merely a loss of chloride but of sodium and chloride. During periods of dehydration there may be a trace of albumin in the urine, but this rapidly disappears when the patient is hydrated. The blood pressures are normal, except in shock, when they are low. No eye ground changes have been noted.

4. Macrogenitosomia, Associated With Adrenal Insufficiency:

Four proved cases of macrogenitosomia associated with adrenal insufficiency have been reported. The case of Wilkens and his associates¹⁰ satisfactorily demonstrated that hyperplasia of the androgenic zone can encroach on the "true" cortex.

Without signs of abnormal genital development it may be impossible during the first few weeks of life to distinguish between the cases reported here and those associated with hyperplasia of the androgenic zone. With the appearance of a deep voice, pubic hair, pigmentation of the skin, or macrogenitosomia, the diagnosis becomes obvious. Patients with hyperplasia of the androgenic zone of the adrenals, without adrenal insufficiency, may not reveal precocious sex development until a year or two of age. All of the patients associated with

adrenal insufficiency had abnormal enlargement of the penis and other signs of virilism at 6 months of age or before. At the time of this writing, our youngest patient is 7 months and the oldest, 35 months of age, and still there is no evidence of virilism.

I do not feel that a moderate increase of 17-ketosteroids in the urine necessarily indicates the existence of hyperplasia of the androgenic zone. The increased amounts of this steroid in two of the patients may be caused by a transient hyperfunction or temporary hyperplasia of an otherwise normal adrenal in an effort to compensate for the D.C.A. deficiency. If large amounts of 17-ketosteroids were continuously excreted, precocious sex development would most likely occur. In the absence of macrogenitosomia, we are probably justified in making a diagnosis of a true hyperplasia of the androgenic zone only when there are repeated demonstrations of high levels of urinary 17-ketosteroids.

The negative family histories and the fact that treatment can eventually be discontinued without return of symptoms are other important distinguishing characteristics of the patients reported on in this paper.

5. *Addison's Disease*: The young age of these patients, the lack of skin pigmentation, and the failure to demonstrate deficiency of the carbohydrate metabolism should cause no confusion in diagnosis. Only four cases of Addison's disease in patients below 5 years of age have been reported.¹²

Only the uncomplicated cases requiring prolonged hospitalization have been presented; however, infants with this syndrome who have superimposed infections of varying severity, particularly diarrhea, are probably the most common but also the most difficult to detect. The symptoms caused by a lack of the D.C.A. factor are those that can be readily ascribed to any illness in a young baby. To add further to the difficulty in diagnosis is the fact that the usual type of parenteral fluid therapy is in large measure all that is required during periods of low adrenal function. The pathologist is of little assistance in the diagnosis of a functional disturbance of the adrenal glands. These are the reasons why this syndrome has gone unrecognized.

There is experimental evidence suggesting that the giving of adrenal hormones produces atrophy of the adrenal glands. After D.C.A. was required for over one year in Cases 1 and 2, I began to wonder if this were not true; however, since this steroid could eventually be discontinued without evidence of recurrence of the symptoms it seems quite evident that there has been no permanent damage to the adrenal glands.

When added salt and D.C.A. are given to infants not showing this syndrome there is little or no change. When a weight gain is artificially produced by this means, there is a tendency to development of edema, and the serum chloride is elevated to an abnormal value. In the cases reported here the blood chemistry returned to normal and remained so during further administration of salt and D.C.A.

Degenerative lesions in the arterioles of the brain, kidneys, and heart in experimental animals have been attributed to the use of D.C.A. and salt.²³

Recent experimental work of R.G. Harrison,²⁴ however, suggests that D.C.A. and salt may not be responsible for these changes but may even protect the animal against such changes.

No harmful effects have been noted in the patients described in this paper. The failure to develop hypertension, the lack of edema, the normal hearts, the negative fundus examinations, and the clear urine are further evidences that the steroid, plus sodium chloride in the amounts prescribed, caused no damage.

Because of the physiologically low renal activity during early life, D.C.A. and salt may cause further depression of this function. It is also theoretically possible to cause atrophy of the adrenal cortex following unwarranted and prolonged administration of the hormone. Therefore, desoxycorticosterone acetate should be used only when and where adequate facilities for following the blood chemical changes are available.

CONCLUSIONS

1. A syndrome is presented in young infants which is characterized by nausea, regurgitation, vomiting, eventual dehydration, and collapse, accompanied by excessive renal loss of sodium, chloride, and water.

2. This syndrome is thought to be caused by a temporary absence or physiologic low supply of the desoxycorticosterone factor of the adrenal glands.

3. Adrenocortical hormones and salt are of specific therapeutic value in this disorder. Therapy can eventually be discontinued.

4. Milder degrees of the deficiency are thought to exist.

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CONSTITUTIONAL STATURAL OVERGROWTH AND INCREASED LOWER BODY SEGMENT WITH NORMAL SEXUAL DEVELOPMENT IN A FAMILY OF FOUR

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IN THE newborn child the measurement of the trunk or upper body segment, taken from the top of the pubis to the top of the head, will be found to be greater than the measurement of the lower body segment, taken from the pubis to the heel, by as much as 5 inches. As time goes on, and as the normal infant grows older, the lower measurement gradually approaches the upper measurement, until at about the age of $10\frac{1}{2}$ to 11 years, if he is still normal in development, the lower measurement is almost equal to the upper measurement. Finally, as the child approaches the age of 14 to 15 years, and then thereafter into adulthood, the lower measurement in the male exceeds the upper measurement by about one inch, and, in the female, the upper measurement exceeds the lower by about one inch.^{1a}

Where there is abnormal genital development, such as with hypoplasia or cryptorchidism, there will be a derangement of these body measurements, especially, if the abnormalities had their inception in early infancy. The extent of the skeletal disproportion depends upon the type and severity of the endocrine disturbance, the age of the patient when the disturbance had its onset, and the length of time it has been in existence.

I have found that an increased lower body segment may be found in boys with gonadal insufficiency regardless of whether these boys present normal, accelerated, or depressed total linear height, whether the patients present an adipose or nonadipose type of genital dystrophy, and whether the origin of the gonadal insufficiency is pituitary, primary gonadal, or thyroid. In the cretin, where growth in general is interfered with severely and where linear growth specifically and most other developmental processes are practically at a standstill, one may not find an increased lower body segment.^{2a, b, c}

Where the gonadal insufficiency has existed since infancy in any of the types of cases enumerated above, I have noted, after treating and studying many such endocrine cases over many years, that lower measurements are equal to the upper measurements at about the age of 6 or 7 years instead of at the age of $10\frac{1}{2}$ or 11 years as in the normal; and that, thereafter, the lower measurements eventually surpass the upper measurements, not by an inch or so as in the normal male, but by 4 inches or even by as much as 7 inches or more. That is, the skeletal disproportion is similar to that seen in eunuchism or eunuchoidism which has existed since early infancy—so-called eunuchoid skeletal proportions.

Generally, eunuchoid proportions found in a patient indicate that a gonadal deficiency exists or had existed. In other words one usually assumes that the two conditions accompany each other.

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I have found, however, that this is not always true. A state of gonadal insufficiency should not always be assumed on this basis alone. Additional confirmation should be present.

I have found, as have other writers as Bauer,³ b Shelton,⁴ and Mansbacher,⁵ that so-called eunuchoid proportions can exist without any accompanying state of gonadal insufficiency.

In my work, I have had the occasion to study a family of four—mother, father, and two brothers, the latter for many years—who all showed tallness or statural overgrowth and increased lower body segments or so-called eunuchoid skeletal body proportions, but who did not have the gonadal insufficiency or the accompanying genital underdevelopment usually associated with such eunuchoid skeletal proportions.

Because such cases exist and because they should be recognized without any of the stigma of eunuchoidism attached to them, I am presenting the development data of the two boys in detail, as well as the pertinent facts in the development of the mother and father.

CASE REPORTS

CASE 1—(Fig. 1) R H O at 18½ years of age was 75½ inches in height and weighed 200 pounds, with the lower body measurement greater than the upper by 7 inches.

His infantile and childhood history was uneventful and normal; the only exception was that he was a tall infant and was always the tallest boy in his class.

At 12 years, 9 months of age, his height was about 70 inches, so that he fell within the 1 to 10,000 percentile group on Burgess' growth chart (that is, he was taller than about 10,000 others of the same age group).⁶ His lower measurement was 39 inches while his upper was 32 inches. At this time, he was showing normal puberal changes, and his voice was becoming gruffer.

At 13 years, 7 months his linear height was 72 inches, an increase of about 2 inches within ten months, and his lower measurement exceeded the upper measurement by about 7 inches. Roentgenograms of the carpus showed all epiphyses to be open. The sella turcica was of moderate size and showed some tendency toward bridging. The gonads and external genitals were well developed.

At 14 years, 2 months of age, his height was 74½ inches, an increase of 2½ inches in seven months; the lower measurement still exceeded the upper measurement by 7 inches. The epiphyses of the hand and wrist were still open. He had occasional nocturnal and diurnal emissions and was self-conscious.

At 15 years, 4 months of age, his linear height was 75½ inches, an increase of 1½ inches, and the lower measurement still was 7 inches greater than the upper measurement. The epiphyses of the carpus were practically closed. Sexually, from the appearance of the genital apparatus, he was matured.

At 16 years, 2 months of age, after a ten months' lapse, his linear height showed no increase, it was still 75½ inches; and his lower measurement still exceeded the upper measurement by about 7 inches. The patient's height now fell within about the 1 to 7,000 group on Burgess' growth chart. The epiphyses of the carpus now were united; the distal epiphyses of the radius were normal and were not completely closed (Fig. 2).

Other findings. His feet required a 14½ shoe. There were some hammer toes. He required a 10½ glove and 16½ size collar. He presented no prognathism. He was mentally alert and, as mentioned before, sexually mature.

⁶Shelton's case of "Constitutional Statural Overgrowth," as quoted by Friedgood, is that of a boy 18 years old with a total linear height of 77½ inches who presented eunuchoidal skeletal proportions. Although this boy presented "normal external genitalia," there was absence of body hair, transverse pubescence, poor libido and unusually "small prostate." It is likely that this patient has had or still has some gonadal insufficiency which accounts for his skeletal makeup and for the disturbed sexual symptoms. I do not think this patient similar to the family I am reporting.

At the last examination, when the patient was 18½ years of age, the findings were the same as upon the examination when he was 16 years, 2 months of age. No changes had taken place.

CASE 2.—D. H. O., the younger brother (Fig. 1), at 16 years of age, weighed 185 pounds, and was 77½ inches in height, with the lower measurement greater than the upper by 6½ inches.

His infantile and childhood history was normal, with the exception that there was thought to be a slight delay in the development of the ossification centers when the patient was 5 years of age. He, too, was always the tallest in his class.



Fig. 1.—The two brothers, D. H. O. and R. H. O., at ages 16 and 18½ years, respectively. Note increased lower body segment and normal external genital development.

At 11 years of age, his linear height was 66½ inches, so that he fell within the 1 to 10,000 percentile group on Burgess' growth chart. His lower measurement exceeded the upper by 5 inches. The slight delay in ossification noted at the age of 5 must have corrected itself; it was not apparent at this time. None of the epiphyses of the carpus were as yet united, and the sella turcica was of moderate size with a tendency toward bridging. Mentally he was normal, but physically there were signs of the early onset of puberty.

At 12 years, 9 months of age, his linear height was 72 inches, an increase of 5½ inches in a period of one year and nine months. His lower measurement exceeded his upper by 6 inches. Roentgenograms of the carpus showed that all the epiphyses were still ununited. At the elbow, the capitellum and trochlea were just uniting. The gonads and

external genitalia were developing normally, axillary and pubic hair was present in moderate quantity, and hair on the upper lip was beginning to appear. His voice was breaking, and he showed evidences of puberal change.

A B. M. R. taken at this time was -17 per cent. He, therefore, was given some desiccated thyroid, but this medication was taken irregularly and only for a short time.

At the age of 13½ years, he weighed 158 pounds and his linear height was 74½ inches—an increase of 2½ inches within nine months, still placing him within the 1 to 10,000 percentile group on the Burgess' growth chart. At this time his lower body measurement exceeded the upper measurement by 7 inches. All the epiphyses of the carpus were still open. His voice had become gruffer, and he was showing normal sexual as well as normal mental development.

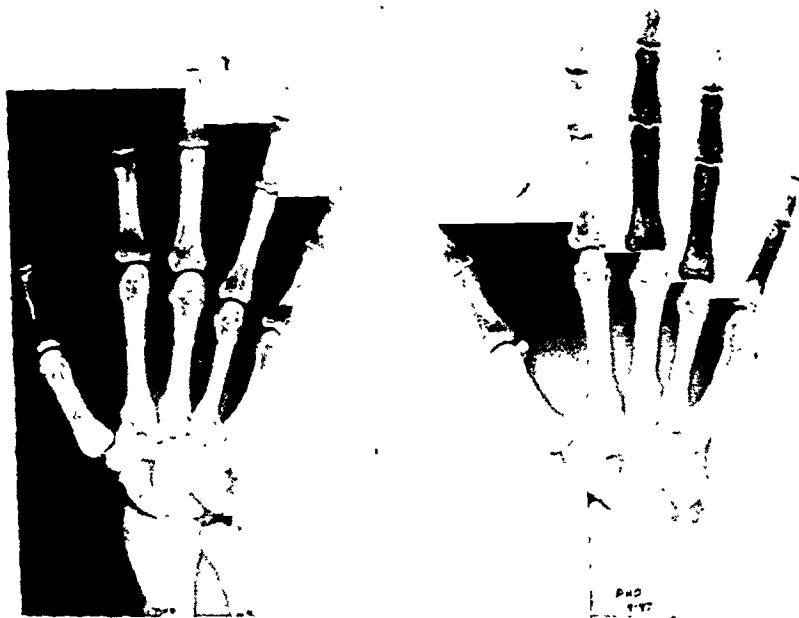


FIG. 2.—Roentgenograms of the two brothers, D. H. O. and R. H. O., at ages 16½ and 19 years, respectively. Note the normal bone development and epiphyseal closure for age.

At 16 years of age, this patient was 77½ inches in height, a gain of 3¾ inches in eighteen months. The lower measurement exceeded the upper by about 6½ inches. Roentgenograms of the carpus at this time showed that all epiphyses were closed, although there was still a faint separation on the lateral aspect of the epiphyses of the distal radius and ulna (Fig. 2). Linear growth now was apparently completed. The genital apparatus was normal, and the normal sexual reactions for his age were taking place. The face showed some acne, and the voice now definitely had adult pitch. Puberty had been accomplished.

Other findings: He wore a size 14 shoe and about a size 9 glove. His collar size was about 14½. He showed no prognathism.

CASE 3.—The father, aged 47 years, is 72½ inches tall and weighs 220 pounds.

His lower measurement exceeds the upper by 4 inches.

Childhood history was normal.

The size of his shoe is 11, the glove is 9, and the collar size is 17.

He shows normal mental development, and there is no evidence of physical or sexual disturbances having existed at any time.

CASE 4.—The mother is 69½ inches tall and weighs 158 pounds. Her lower measurement is 6 inches greater than the upper.

Childhood history was normal.

She wears a size 10 shoe, and size 8 glove.

She shows normal physical, mental, and sexual development.

COMMENT

An accelerated height of 70.2 inches or over is considered by Engelbach^{1b} to be a disturbance attributable to an overactive anterior pituitary gland. As such, my cases fall within this grouping, with the exception of the mother who is tall but not quite that tall, although she too presents the same excessively increased lower body segment as the others.

While I agree that an overactivity of the anterior pituitary gland is perhaps likely in these cases, I feel that one must not overlook the following facts: Firstly, statural growth for this generation is on the whole greater than that for individuals a generation ago. Secondly, none of my patients shows any evidence of an enlargement of the sella turcica, nor do the parents or the older brother, whose epiphyses have now been closed for several years, show any evidence of acromegaly.

In all likelihood, therefore, I believe that the tallness or statural overgrowth in these four adults is due simply to a functional or physiologic overactivity of the somatotropic factor of the anterior pituitary gland and is not due to a pathologic overactivity, as in acromegaly. It seems to me that there was simply a familial trend toward this statural overgrowth.

Further, it is this familial trend that can also account for the excessively increased lower body segment in these patients without the usual accompanying manifestations of gonadal insufficiency.

That there was no gonadal insufficiency was indicated not only by the normal appearance of the sexual apparatus and the apparently normal sexual response in all of these individuals, but also by the fact that the two brothers showed epiphyseal closure at the proper time—an indication that normal gonadal secretion was present. Had gonadal development been deficient or arrested, the epiphyses would have remained ununited for a long time and would have shown up on roentgenograms.

While my patients showed definite evidence of normal gonadal development and function, there may be cases where gonadal insufficiency may not be apparent or may go unrecognized. Such a case where gonadal insufficiency may not have been apparent but will, I believe, eventually make itself evident because of the familial trend in that direction, is that described in Mansbacher's report on "Familial Eunuchoid Gigantism"^{1c} in two brothers.

Here, the younger brother, aged 10, presented a marked overgrowth of the long bones and eunuchoid skeletal proportions, and yet he showed no apparent sexual underdevelopment. The older brother, aged 19, was 83 inches tall and also presented similar skeletal disproportions and open epiphyses, but he showed the usual accompanying sexual underdevelopment, as well as hypotrichosis, impotence, and absence of secondary sex characteristics.

There is good reason to believe from the developmental report, that Mansbacher's younger boy, who at 10 years of age did not show any marked evidence

of any sexual disturbance, will eventually follow the pattern of sexual underdevelopment similar to that of his older brother, just as the younger brother in the family I have presented followed the developmental familial trend of his older brother and his parents.

In my cases, I wish to point out that I am using the term eunuchoid with reservations and that I am, therefore, limiting it only to a disproportion between the upper and lower body segments. It carries with it no connotation of sexual underdevelopment.

SUMMARY AND CONCLUSIONS

I have found that skeletal growth and body proportions usually are altered when there is a gonadal insufficiency from early infancy. At the age of 6 or 7 years, instead of at 10½ or 11 years as in the normal, gonadal insufficiency will cause the measurement of the lower body segment to become equal to the measurement of the upper body segment. Thereafter, if the gonadal deficiency continues, eunuchoid skeletal proportions become apparent—that is, there will be noted an increased lower body segment and a delay in closure of the epiphyses of the long bones.

Thus, generally, it can be said that so-called eunuchoid proportions or increased lower body segment can be attributed to gonadal insufficiency.

In my cases of the two brothers and their parents, gonadal insufficiency does not exist.

It becomes necessary, therefore, to recognize that there is a skeletal disproportion similar to that noted in patients with gonadal insufficiency, which must be attributed simply to a constitutional, genetic, or familial factor rather than to gonadal failure.

It is suggested that instead of the word eunuchoid one should use "increased measurement of the lower body segment" or "increased lower body segment or measurement" so that no connotation of sexual underdevelopment goes along with it.

There must exist many cases similar to mine. I have reported these because to date such reports have not been sufficiently emphasized or reported upon in the literature.

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SCLEREMA NEONATORUM

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SCLEREMA neonatorum is an uncommon disease characterized by a diffuse, rapidly spreading, nonedematous, tallowlike hardening of the subcutaneous tissue of infants in the first few weeks of life. The skin in involved areas cannot be picked up, and the subcutaneous tissue seems bound down to subjacent muscle and bone. The involvement usually starts on the buttocks, thighs, or trunk, but may spread to involve any area of the body save the soles, palms, and genitalia. The affected infants often have other diseases associated with the process, such as pneumonitis, enteritis, intracranial hemorrhage, or congenital heart disease. Of the reported cases, only a minority are in premature infants. Many show marked difficulty with respect to temperature control and little tendency to spontaneous movement, especially after the process is well established. The disease is usually discovered in the first few days after birth, but may be seen immediately post partum or as late as several weeks of age. With few exceptions, the course is rapidly downhill with a fatal termination only a few days after appearance of the manifestations.

This condition was probably first described by Usembenzius,¹ but the classic description of the disease was by Underwood.² He named the disease descriptively "skin-bound," giving such a thorough and exact picture of the condition that the process is called "Underwood's Disease" in many texts today. Unfortunately the introduction of the term "sclerema"^{3, 4} brought about a confusion in nomenclature that still persists.

Standard references⁵⁻⁷ agree that sclerema is a separate entity clinically and pathologically from such diseases as subcutaneous fat necrosis and scleroderma. Despite this, many authors have applied the term "sclerema" to subcutaneous fat necrosis^{8, 9} or have combined subcutaneous fat necrosis and sclerema under the single term "sclerema neonatorum."^{10, 11} Still others^{12, 13} include scleroderma of later infancy and childhood. One author,¹⁴ in an attempt to clarify the nomenclature, described a case of hydrops fetalis as sclerema. Even Channon and Harrison,¹⁵ whose chemical studies of both sclerema and fat necrosis have been fundamental, combined both diseases under the single term although they admitted that others might disagree with such a classification. One article¹⁶ dismisses sclerema altogether as being "nothing more than subcutaneous fat necrosis present at birth."

Bernheim-Karrer¹⁷ has established the term "subcutaneous fat necrosis" first suggested by Fabry¹⁸ and has applied it to a definite process distinct from sclerema. Other authors¹⁹⁻²¹ have since preferred to employ this term. Eichenlaub and Sandler,²² in reporting a case of sclerema, believed that there are five separate similar entities affecting the infant, i.e., edema, scleredema, scleroderma, sclerema, and subcutaneous fat necrosis. Their differentiation of the latter two,

which is distinct, is based on the clinical pictures, histologic findings, and prognoses. The authors whose cases are included here under the review of cases have used the term "sclerema" as outlined in the introductory paragraph.

Clinically subcutaneous fat necrosis may be differentiated from sclerema. The former occurs in more or less sharply circumscribed areas which are freely movable over subjacent muscle and bone and have a marked tendency to calcification and cyst formation. The process shows a predilection for the cheeks, shoulders, and back. The infants affected have little or no difficulty with temperature control or spontaneous movement. There is usually a history of obstetric or other trauma to the involved areas. As the disease progresses, the areas have a tendency to liquefy and in most instances to disappear. The prognosis is good; almost all patients recover. Section of affected tissue shows neutral fat crystals with infiltration of lymphocytes, plasma cells, and giant cells, a picture not seen in typical sclerema.

REVIEW OF CASES

In reviewing the cases reported in the literature as sclerema, the authors have eliminated all cases which seem more typical of subcutaneous fat necrosis, scleroderma, or hydrops. Also, nine probable cases²⁷⁻³¹ lack sufficient information to warrant inclusion on the chart. Only cases which conform to the criteria described in the opening paragraph are included.

Briefly, the significant findings from the twenty-eight cases reviewed (including the probable cases not shown in the table) are as follows: (1) Average age of onset was 4 days with extremes from birth to 70 days; (2) 25 per cent of the mothers were ill at the time of delivery; (3) all but two deliveries were spontaneous; (4) average birth weight was 2,800 Gm. with variations from 2,150 to 4,100 Gm.; (5) the majority of infants exhibited abnormal behavior at birth, weakness and cyanosis being the most common symptoms; (6) almost all children had difficulty with body temperature control and evidences of other complications besides sclerema; (7) 75 per cent died, with the average age of death 10 days; (8) eleven infants were autopsied, thickening of connective tissue bands being the most common finding.

CASE REPORTS

CASE 1.—B. B. M., a 2-day-old Negro male infant, was transferred to the pediatric service Feb. 24, 1947, because of "difficult respirations." The mother was 24 years old, seronegative, Rh positive, and in good health. One previous pregnancy resulted in a full-term, healthy infant, and she had a negative past history for syphilis, tuberculosis, and diabetes. Labor had been normal and lasted twelve hours. The presentation was vertex, L.O.A. Delivery was spontaneous. The birth weight was 2,700 Gm. The child did not breathe spontaneously and required suction and intramuscular caffeine sodium benzoate. After entering the regular nursery, the child's respiration continued to be grunting. The following day a laryngoscopy was performed, but nothing abnormal was seen. He had taken a negligible amount of fluids by mouth before admission.

Physical Examination.—Examination revealed a well-nourished newborn infant who appeared desperately ill. The respirations were grunting, gasping, and irregular. There was cyanosis of the hands and feet but no jaundice. The rectal temperature was 95° F. The subcutaneous tissue over the back, buttocks, thighs, and legs was markedly indurated and bound down to underlying structures. The skin was cold and could not be picked up. There

TABLE I. REVIEW OF C

AUTHOR AND YEAR	COLOR AND SEX	AGE AT ONSET (DAYS)	PAST OBSTETRIC HISTORY OF MOTHER	MOTHER'S CONDITION	LABOR AND DELIVERY	BIRTH WEIGHT (G.M.)	CONDITION AT BIRTH	CONGENI- TAL ANOMALY
1. Ballantyne ⁶⁵ 1890	W. M.	2	Primipara	Healthy	Spontaneous normal labor	2,150	Weak respira- tions	None
2. Northrup ⁶⁸ 1890	W. F.	5	-	-	-	-	-	One of two
3. Knopfmacher ¹⁴ 1897	W. F.	23	Primipara	Healthy	Spontaneous normal labor	-	Good	None
4. Knopfmacher ¹⁴ 1897	W. F.	4	Primipara	-	Spontaneous normal labor	3,000	Good	None
5. Taylor ⁶⁷ 1900	W. M.	At birth	Several full term, one miscarriage	-	Normal	-	Feeble, cyanotic	None
6. Stillman ⁶⁹ 1903	W. M.	7	-	Healthy	-	"Full term"	Cyanotic	None
7. Sarnovat ⁷¹ 1906	W. F.	2	4 0 0 3* 1 died, age 1 day	Eclampsia	-	-	Fever, weak- ness	None
8. Sedgwick ⁴⁹ 1911	W. M.	10	1 1 0 11*	-	-	2,500	-	None
9. Paterson ⁴⁵ 1912	W. M.	2	- 0 0 2*	Healthy	Spontaneous labor 4 hours	3,650	Cyanosis, convul- sions	"Some ce- bellar lesion"
10. Hodder ⁴⁶ 1920	W. M.	At birth	2 0 0 2*	Anemia, hemorrhage, placenta previa	Spontaneous after 2 pituitrin injections	-	Cyanotic	None
11. Bourne ⁶⁷ 1922	W. M.	5		Healthy	-	2,500	Sucked poorly	None
12. Nash ¹⁷ 1924	W. F.	2	Primipara	Bacilluria	Compression of cord	3,750	Cyanotic	None

*Numbers in order shown refer to parity, miscarriages, premature, and living children.

SCLEREMA NEONATORUM

DEPENDENCE OF CLINICAL COURSE	COMPLICATIONS	BODY TEMPERATURE CONTROL	INVOLVEMENT	LABORATORY DETECTION	THERAPY	OUTCOME	AUTOPSY FINDINGS
e	None	Poor	"Almost universal"	-	-	Died 3 days	Atrophy of fat cells; increased width of connective tissue bands
ie	None	Rectal temperature too low to register	Thighs, arms, cheeks, trunk	-	None	Died 9 days	"No gross nor microscopic pathology"
ie	Sepsis (umbilical abscess)	Poor, "very low"	Extremities	Fat: melting pt., 44° C.; solid, pt., 36° C.; I. no., 38.5	-	Died 25 days	-
-	Probable sepsis	First elevated, then depressed	Extremities, thorax	Fat: melting pt., 43° C.; solid, pt., 36° C.; I. no., 39.7	-	Died 25 days	Umbilical arteritis
-	Bradycardia	Poor—low	Trunk, head	None	Olive oil emulsions	Died 5 days	-
me	None	Fever and hypothermia	Extremities, trunk, genitalia	Blood count normal, culture sterile	Hot baths	Died 11 days	Lack of subcutaneous fat; otherwise, normal
me	Icterus	Fever 38.5° C.	Extremities, trunk	-	Incubator	Died 7 days	No cellular increase; a layer of fibrohyaline fascia under skin
one	Icterus	Poor—low	Extremities	Muscles had high percentage of fat	-	Died 14 days	No microscopic pathology
isability of left arm and hand	None	-	Legs, buttocks, then trunk and head	None	Incubator, spoon feeding whisky, digitalis, adrenalin	Survival; disease lasted 15 weeks	-
one	Unable to swallow, intestinal obstruction	Poor—low	Thighs, buttocks, extremities	None	None	Died 9 days	-
one	None	Too low to be registered	Trunk, lower extremities, head	None	Incubator at 40° C., thyroid extract, gray powder, rectal NaHCO ₃ enema	Survived	-
one	None	Adequate	Extremities, back of trunk	None	Hot baths, gray powder	Survived; disease lasted 6 months	-

AUTHOR AND YEAR	COLOR AND SEX	AGE AT ONSET (DAYS)	PAST OBSTETRIC HISTORY OF MOTHER	MOTHER'S CONDITION	LABOR AND DELIVERY	BIRTH WEIGHT (GM.)	CONDITION at BIRTH	CONGENIT ANOMALI
13. Harrison & McNee ⁴⁸ 1926	W. ♀.	70	1 0 0 1*	Healthy	-	-	Good	None
14. Condon ⁷² 1930	W. M.	1	3 0 0 3*	Pneumonia	-	2,250	Good	None
15. Allyn & Marek ⁵⁰ 1933	W. ♀.	1	2 0 0 2*	Pre- eclampsia	Spontaneous easy labor	-	Cyanosis	Enlarged thymus
16. Eichenlaub & Sand- ler ²² 1937	N. F.	4	9 0 0 9*	-	"Normal"	4,100	Good	None
17. Hughes & Hammond 1948	N. M.	2	2 0 0 2*	Healthy	Spontaneous	2,700	Difficult respira- tions	Microceph. ? enlarge thymus & congenita heart dis
18. Hughes & Hammond 1948	N. F.	2	4 0 0 4*	Healthy	Mid-forceps	2,600	Difficult respira- tions, obstetric palsy	None
19. Hughes & Hammond 1948	N. F.	33	2 0 0 2*	Healthy	Spontaneous	2900	Good	None

*Numbers in order shown refer to: parity, miscarriages, premature, and living children.

was no pitting on pressure anywhere on the body. There were frequent generalized tonic-clonic convulsions. The head appeared small with a small anterior fontanel. Its circumference (occipitofrontal) was 31.5 cm. while the chest circumference was 32.0 cm. The child's length was 48 cm. There was a bloody serous nasal discharge. The chest was asymmetrical with a bulge in the costal cage over the precordium. The lungs were relatively dull to percussion and sounded poorly aerated. The heart was enlarged; its sounds were of fair quality. There was a loud, long systolic murmur heard best along the left sternal border. The remainder of the examination revealed nothing abnormal.

Laboratory Findings.—Leucocytes numbered 17,200, and there were 17.4 Gm. of hemoglobin. The urine was negative. The blood serology was negative. Analysis of the blood serum revealed a carbon dioxide content of 27.2 volumes per cent, chlorides 113.6 mM per liter, calcium 7.9 mg. per cent, and phosphorus 6.6 mg. per cent. Cultures of the blood and spinal fluid were negative. Roentgenograms of the chest showed a diffusely enlarged heart and possibly enlarged thymus (Fig. 1). Films of the long bones were negative.

CONT'D

INCIDENCE OF TRAUMA	COMPLICATIONS	BODY TEMPERATURE CONTROL	INVOLVEMENT	LABORATORY DETERMINATION	THERAPY	OUTCOME	AUTOPSY FINDINGS
one	"Ileocolitis"	Fever	Trunk, extremities	-	-	Died 13 weeks	Increase in size of fibrous trabeculae, atrophy of fat cells
one	Bloody snuffles	Poor—low	"Entire body"	-	-	Died 4 days	-
-	-	-	Thighs, legs, then universal	-	Hot baths, oil rubs, ipecac, radiation to thymus	Survived	-
one	Bilateral otitis, pneumonia, subcutaneous fat necrosis	-	Legs, then entire body	-	-	Died 27 days	Pathology that of coexisting subcutaneous fat necrosis
one	None	Poor—low	Entire body except palms, soles, genitalia	Acidosis hypocalcemia, blood sterile, enlarged heart	Hot baths, oxygen, roentgen radiation to thymus, parenteral support	Died 6 days	-
Obstetric palsy, left	Intestinal obstruction	Normal	Trunk and extremities	Acidosis, blood sterile	Hot baths, oxygen, suction, parenteral support	Died 3 days	Distention of fat cells, thickening of connective tissue bands; no cellular infiltration
None	Diarrhea, gangrene of feet, ankles, fingers	Slight fever	Trunk and extremities	Slight acidosis and hypocalcemia	Parenteral support, oxygen	Survived	Thickening of connective tissue bands in area of resolved sclerema

Therapy.—On admission the child was placed in constant oxygen. He was supported parenterally with subcutaneous injections of one-third M/6 sodium lactate and two-thirds physiologic saline mixed with 5 per cent glucose in distilled water. Because of cardiac enlargement, he was not given intravenous fluids, and subcutaneous injections were by necessity given over the anterior thorax and abdomen. His daily fluid intake was slightly more than 100 c.c. per kilogram. He received a small amount of formula by mouth. He was given 70 R to his upper chest on the second day in hopes of reducing the size of the thymus gland. From the second day, for fifteen minutes every three hours he received hot water baths, at a temperature between 100° and 105° F., which covered the whole body except the face, which was covered by an oxygen cone. Between the baths he was kept under a heat lamp.

Clinical Course.—On oxygen and heat therapy the aeration of the child's lungs improved and convulsions ceased. However, there was marked difficulty with temperature regulation, the rectal temperature falling as low as 95° F. despite external heat. There was never any fever. The induration of the subcutaneous tissue progressively spread to involve the entire

body except the palms, soles, and genitalia. With its spread, the child developed greater difficulty sucking and breathing and displayed less and less spontaneous movement until he appeared to be cast en bloc. There was never any diarrhea or signs of intestinal obstruction. The course was progressively downhill with death on the sixth day of life. There was no autopsy.



Fig 1—Roentgenogram of chest (Case 1) showing diffusely enlarged cardiac (and possibly thymic) shadow. Cardiothoracic index is 0.50.

CASE 2—B. G. R., a 2 day old Negro female infant, was transferred to the pediatric service May 9, 1947, because of "inability to use left arm and peculiar hardness of skin." The mother was 21 years old, seronegative, Rh positive, and in good health. Three previous pregnancies all resulted in full term, healthy infants. She had a negative past history for syphilis, tuberculosis, and diabetes. Labor had been normal and lasted twelve hours. Due to a pelvic dystocia caused by a small sacral exostosis, the head lay in a persistent L.O.T. position, was rotated L.O.A., and delivered by a mid forceps procedure. The child did not breathe spontaneously, but was resuscitated after several minutes and then breathed poorly. She was laryngoscoped, and thick mucus was removed from her upper respiratory tract. After this she breathed fairly well and slowly gained muscular tone. The birth weight was 2,600 Gm. Shortly after birth, it was noted that the child had suffered a brachial palsy of the upper arm type on the left. The day after birth the child was noted to be vomiting and failed to pass any meconium. On the day of transfer, the baby was unable to retain any fluids whatsoever. She still had failed to pass any meconium and also had developed a "wooden" texture to the subcutaneous tissue of the trunk and left buttock.

Physical Examination—Examination revealed a well developed and nourished newborn Negro female infant who appeared acutely ill. The cry was weak, but the muscular tone was good except for the left arm. Respirations were regular and not labored. There was no cyanosis or jaundice. The child did not convulse. The subcutaneous tissue of the trunk and left buttock was firm and bound down to underlying structures. The skin was cool and could not be picked up. There was no pitting on pressure. The only evidence of forceps trauma was a swelling of the lids of the left eye. The lungs were fairly well aerated, and the heart was not enlarged. The heart sounds were of good quality, and there were no murmurs. The abdomen was soft but slightly distended, and was quiet to auscultation. The

anus was patent, and rectal examination failed to reveal any obstruction. The remainder of the examination revealed nothing abnormal.

Laboratory Findings.—Blood count: 4,900,000 red cells, 18.0 Gm. of hemoglobin, 11,050 white cells. Smear: 14 per cent non-segmented polymorphonuclears, 50 per cent segmented polymorphonuclears, 36 per cent lymphocytes. Hematocrit 48 per cent. Red cells and platelets normal in appearance. Serology negative. Analyses of blood serum: carbon dioxide content 32.8 volumes per cent, chlorides 78 mM per liter. Cultures of the blood and spinal fluid were negative. The urine was normal. Subdural taps bilaterally revealed a very small amount of clear fluid. Roentgenograms of the abdomen revealed gas-distended small bowel with multiple fluid levels (Fig. 2). There was no gas visible in the large bowel.



Fig. 2.—Roentgenogram of abdomen (Case 2) showing gas-distended loops of small bowel with fluid levels forming ladder pattern. No gas is visible in large bowel.

Therapy.—The child was placed in an oxygen tent. Hot water baths (102°-104° F.) were given for twenty minutes every three hours. In between baths the infant was kept under a heat lamp. Because of persistent vomiting, fluids were discontinued by mouth. In the period of twenty-four hours on the pediatric service the child received 145 c.c. of 10 per cent glucose in distilled water, 50 c.c. of whole blood, 40 c.c. of plasma, and 100 c.c. physiologic saline intravenously. The stomach was washed out by tube, and about 100 c.c. of dark brown watery fluid were removed. Wangensteen suction was instituted along with a rectal tube in order to reduce distention, but was not very successful. The infant was transfused with blood in preparation for surgery to relieve the intestinal obstruction.

Clinical Course.—On the morning following admission the subcutaneous induration was noted to be spreading over the extremities. Despite attempts to rehydrate the patient and to relieve intestinal obstruction, the infant rapidly expired before any operative procedure could be attempted. The child died at the age of 3 days, twenty-four hours after admission to the pediatric service. There was never any difficulty with body temperature control. The child did not have any bowel movements during life.

Autopsy Findings.—On gross examination the external surface of the body revealed only two abnormal findings: (1) a markedly distended abdomen and (2) a firm induration

of the subcutaneous tissue of the face, arms, trunk, buttocks, thighs, and legs. On cut section, the subcutaneous fat depots were unusually thick and firm and had the "feel of suet" when cut.

Internally the pleural spaces were free of fluid. The lungs were normal in size but were slightly heavy, and there were dark, patchy, atelectatic areas of depressed lung tissue seen over the surface of both lungs. Cut section revealed a slight amount of edema fluid mingled with congestive change. The thymus was normal in size. The heart was normal in every respect. The brachial plexus on the left showed some petechial hemorrhage into the capsule, but did not appear torn.

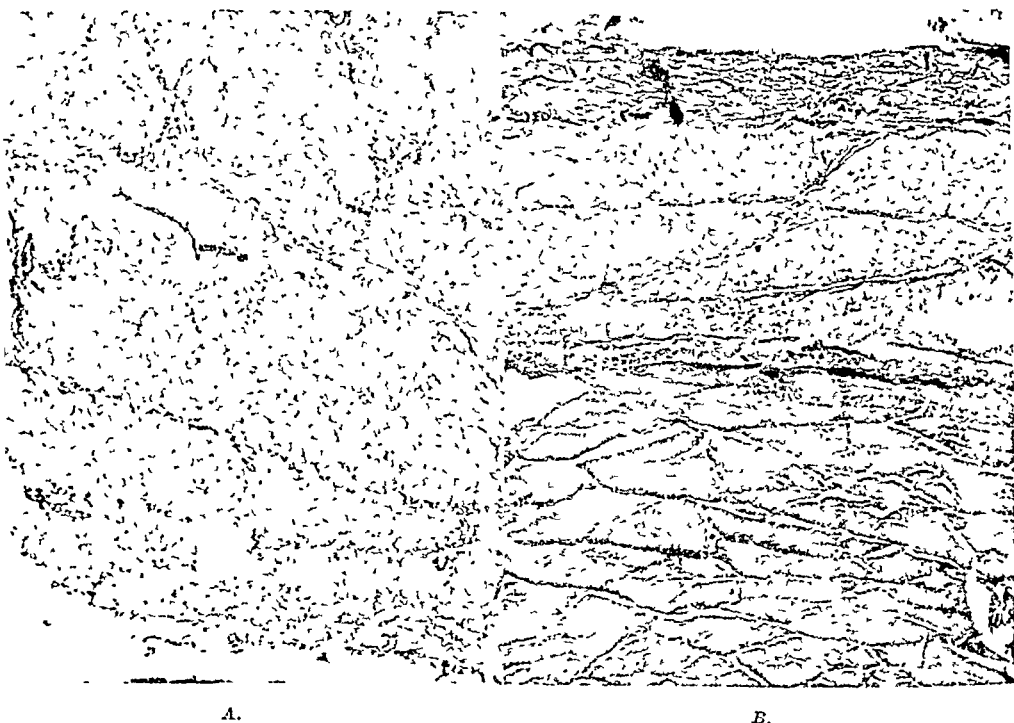


FIG. 3.—A, Shows subcutaneous tissue in Case 2. Compare this with normal control. B, of same age and weight and under the same power of magnification ($\times 30$). Note much greater width of subcutaneous fat layer and increased width of connective tissue bands. Note also lack of cellular infiltration.

On opening the peritoneal cavity, the peritoneal surfaces, liver, spleen, adrenals, and kidneys appeared normal in every respect. The stomach and esophagus were opened and found to be normal except for submucosal hyperemia. The remainder of the small intestines was extremely distended, thin-walled, but without pathologic change in the mucosa. The ileocecal valve was normal and offered no obstruction. The cecum was normal in caliber, but above the junction with the ileum the remainder of the colon was contracted and free of fecal material. No mechanical obstruction of any kind could be discovered, however.

The brain was free of any hemorrhage and appeared normal in every respect.

On microscopic section the subcutaneous fat depots were at least twice as thick as in a normal control of the same weight and age, and connective tissue bands were thicker than those of the control (Fig. 3, A and B). Under higher power, it was seen that the fat cells were engorged with fat, but that there was no cellular infiltration and that the greater size of the connective tissue bands was due to thickening of collagen. By means of the Nile blue staining technique, it was possible to determine the character of this fat. With this stain,

neutral fat stains light red, cerebrosidcs and cephalin light blue, fatty acids and soaps darker blue, and elastic tissue deep blue.²² In these sections the fat stained consistently light red, denoting principally neutral fat deposits. No neutral fat crystals could be detected. The perirenal fat stained purple, denoting the presence of considerable fatty acids, and many fatty acid crystals could be detected in this area. There was also some patchy bronchopneumonia in both lungs on microscopic section. Sections of other organs were not remarkable.

CASE 3.—S. B., a 31-day-old Negro female infant was admitted to the pediatric service July 29, 1941, because of "severe diarrhea." The mother was 27 years old, seronegative, Rh type unknown, and in good health. One previous pregnancy resulted in a full-term, healthy infant. She had a negative past history for syphilis, tuberculosis, and diabetes, but suffered from asthma. Labor had been normal and lasted approximately eight hours. The presentation was vertex and delivery spontaneous. The child cried immediately and exhibited no neonatal difficulties. The birth weight was approximately 2,900 Gm. The child was not breast fed at all, but put on a rather dilute evaporated milk formula with added cane sugar.



Fig. 4.—Gangrene of feet and ankles and three fingers of right hand in Case 3. The right middle finger, which appears gangrenous here, later revitalized.

The baby appeared well until 24 days old (seven days prior to admission) when she suddenly developed severe diarrhea with fifteen green, watery stools a day. The following day the child was taken to another clinic where she was placed on sugar and salt-water mixture. A culture of stool proved negative for intestinal pathogens. After three days of this treatment the diarrhea was considerably improved. An attempt was then made to resume milk feedings, but the diarrhea returned. She was again brought to a clinic where oral sulfadiazine (one grain per pound per day) was prescribed and subcutaneous fluids given. The child's diarrhea did not improve, however, and in the last three days prior to admission to the hospital there were several episodes of vomiting. On the day before admission the mother noted the child was feverish and that there was infrequent, dark, scanty urination.

Physical Examination.—At the time of admission, she was a fairly well-nourished and well-developed infant who appeared acutely ill. The respirations were grunting but not deep. There was no cyanosis. There was moderate loss of skin turgor and depression of the anterior fontanel. There was no evidence of sclerema at this time. The pharynx was moderately injected, but there was no exudate. The lungs were clear to percussion and auscultation. There were no abnormal findings in the heart or abdomen.

Laboratory Findings.—Blood: 5.6 million red cells, 26,600 leucocytes, 72 per cent granulocytes, 13.2 Gm. of hemoglobin. Nasopharyngeal culture showed usual flora. The urine showed no acetone or other abnormalities. Serology negative. Stool cultures failed to reveal any intestinal pathogens. Analyses of blood serum: carbon dioxide content 33.4 volumes per cent; chlorides 104 mM per liter. A roentgenogram of the chest was negative. By August 2 the hemoglobin had fallen to 7.8 Gm. but rose to 11.0 Gm. after transfusion. By August 11 the white blood cell count had dropped to 13,500.

Therapy and Course.—The patient was placed in constant oxygen and given 50 c.c. plasma and 40 c.c. of 10 per cent glucose intravenously, followed by the subcutaneous injection of

tion of 90 c.c. of one third M/6 sodium lactate, two thirds 0.85 per cent saline. This was followed by the oral administration of an electrolyte glucose mixture (containing sodium and potassium chloride, sodium lactate, and glucose), 85 c.c. every four hours. After eighteen hours on this regime, the patient appeared much worse despite some decrease in the number of stools. She was more dehydrated, weaker, and appeared to be more cyanotic. She then received 75 c.c. of 10 per cent glucose followed by 75 c.c. of one third M/6 sodium lactate, two thirds 0.85 per cent saline intravenously, plus 40 c.c. of the latter mixture subcutaneously. At the end of twenty four hours, despite a fluid intake of 200 c.c. per kilo and a weight gain of 250 Gm., the infant still appeared to be in worse condition. The feet and hands were markedly cyanotic despite oxygen. The reflexes were generally hyperactive with a positive peroneal sign. At this time attempts to obtain sufficient blood for determination of serum calcium were unsuccessful. Ten c.c. of 10 per cent calcium gluconate were given intravenously with no response. Four hours later this was repeated and followed by 5 per cent calcium lactate by mouth every four hours. At this time, the serum calcium was 8.6 mg per cent and the phosphorus, 5.5 mg per cent.



Fig. 5—Section of subcutaneous tissue from an area of resolved sclerema in Case 3 ($\times 60$). Note thickening of connective tissue bands and absence of fat necrosis.

The electrolyte glucose mixture was continued by mouth, but reduced to 50 c.c. every four hours. Three hundred cubic centimeters of a mixture of 3 per cent Amigen and 5 per cent glucose with added potassium were given intravenously daily for the next four days. Vitamin D was given for five days in a dosage of 100,000 units per day.

On the second day after admission (thirty third day of life), the child had developed definite gangrene of both feet and ankles and the fingers of the right hand (Fig 4). In addition to this there was marked diffuse induration of the subcutaneous tissues of the thighs and trunk. The skin could not be picked up, did not pit on pressure, and was bound down to underlying structures. The skin over the indurated areas was otherwise clear. The process rapidly spread to involve all the extremities on the following day. By the fifth day the patient's general condition was improved, despite no change in the sclerema or gangrene, and she was started on feedings of an Alacta* and Dextro Maltose mixture.

*Supplied through the courtesy of Mead, Johnson & Co.

which were slowly increased over a period of a week to an adequate caloric intake. During the next several days, the infant received several small transfusions of type compatible heparinized blood to correct anemia and to prepare for operations.

About five days after the full progression of the sclerematous process, it was noted that the subcutaneous induration was becoming less firm. By the end of ten days, it had practically disappeared. Its resolution was as diffuse as its development. There were no localized areas of softening, cysts, or calcific deposits. By the end of the second week, the skin and subcutaneous tissue except for the areas of gangrene felt normal. The only evidence of the past process was a slight desquamation of the skin over the thorax, which cleared after a few days.

The gangrene of the feet, ankles, and fingers remained unchanged, however. There were sharp lines of demarcation around which deep ulcerations developed. Tissues below these lines were devitalized. Amputation, guillotine type, of the middle third of the left leg was performed on the fifteenth day and of the right leg on the seventeenth day. The fourth and fifth fingers of the right hand self amputated on the twenty third day, leaving a clean cut division at the lines of demarcation. The middle finger, which had appeared gangrenous, became revitalized. By this time, the diarrhea had ceased and the infant was doing well on full feedings.

Surgical Pathology—Microscopic sections taken through the areas of gangrene showed the usual picture of advanced coagulation necrosis and loss of definite structure characteristic of necrotic tissue.

In sections taken well above the area of gangrene where the subcutaneous tissue had recently been subject to sclerema, the connective tissue bands were wider than normal, but the fat cells looked essentially normal and cellular infiltration was absent (Fig. 5).

COMMENT

Certain fundamental considerations in the study of subcutaneous fat in infants with sclerema have been fairly well established. (1) that the subcutaneous fat of infants with sclerema is essentially the same chemically as that of normal infants, (2) that the subcutaneous fat of all newborn infants differs from that of older individuals in having a lower solidification point, and (3) that low body temperature might well be a factor in the induration of this fat.

It has been fairly well accepted that the low oleic acid content of fat in sclerema plus a low body temperature are the major factors in the etiology of this condition. There are several possible objections to this premise, however. Although early workers²⁷⁻²⁸ reported infants with sclerema to have less oleic acid in their fat than controls, recent workers²⁹⁻⁴² have found no appreciable difference between the two groups. Still it is contended⁴³ that the lower level of oleic acid of all infants makes them more liable to fat-hardening with chilling. This is true, but it has been found that the solidification point of this fat is too low (22° to 25° C.) to be a factor.⁴⁴ Furthermore, it has been shown that an ordinary infant's subcutaneous tissue when chilled in the morgue is not nearly as firm as that of an infant with sclerema during life.²⁸ Further objection has been voiced to the cold theory⁴⁵ because the process can occur in utero⁴⁶ and does not affect exposed parts of the body first. In addition to this, not all infants with sclerema have had low body temperatures, some remained fairly normal;⁴⁷ others actually had fever during most of the course.^{27, 48} Also, treatment by the use of external heat greater than body temperature has not met with much success.^{27, 49-51}

In support of the low oleic acid plus low temperature theory, is the fact that the fat itself is firm,²⁵ whether or not changes in other subcutaneous tissues³⁴ lend to the induration. It is also a fact that the composition of this fat makes it more susceptible to hardening on cooling, and there is some difference of opinion²⁶ as to the solidification point of this fat, there being no clear end point. Furthermore, the fact that the fat does not readily reliquefy with heat treatment is insignificant when one considers the supercooling properties of fat⁵² and the wide difference between solidifying and melting points which makes it as difficult to reliquefy as to solidify initially. The liquefaction levels reported⁵³ (42° to 44° C.) are above the temperature of baths and other heat agents used in therapy. Also, the fact that cases without low body temperature have been reported loses significance when one considers that it is the peripheral and not the rectal or mouth temperature that is important, and that an infant with moderate fever may have considerable reduction of the peripheral temperature, as is often seen in cases of infantile diarrhea with shock.

Rather than considering olein content, the iodine number of separated fatty acids has been considered a more reliable indication of fat hardness.⁵⁴ A lower fatty acid iodine value has been found in newborn infants than in adults,^{55, 56} but no lower in infants with sclerema than in controls. However, this assumption is not valid. It has been shown that small amounts of palmitic or stearic acid added to other known fatty acids can appreciably affect the melting point with little change in iodine number. The fatty acid content of the fat of newborn infants has also been shown to be higher than in adults, but there is no difference between infants with sclerema and controls. The fact that typical sclerema seems limited in its onset to the first three months of life³⁴ seems significant.

It has been found that the fat of newborn children becomes less hard when the infant begins to feed, becoming richer in olein and the glycerides of volatile fatty acids.⁵⁷ Studies of infant chyle⁵⁸ show that softer fat enters the infant's circulation from the intestinal absorption of milk fats and is presumably the major factor in bringing about this change. It has also been shown that the blood of infants with sclerema has a higher lipid content than that of controls,⁵⁹ suggesting that there may be some abnormality of fat metabolism concerned in sclerema.

Furthermore, it has been demonstrated that maternal diet can influence the hardness of fetal fat,⁶⁰ although the deficiencies in the maternal dietary intake would necessarily have to be rather unusual. Nevertheless, it has been considered a possible factor in sclerema.²⁷ Studies in animals⁶¹ have indicated that fetal fat laid down in a "high temperature zone" of the mother has a high content of saturated fatty acids and, consequently, a high melting point.

At one time dehydration was considered as the major factor⁶² in sclerema neonatorum, and it is true, on reviewing the cases, that most of the infants with sclerema have suffered from some degree of dehydration. But so many infants suffer from severe dehydration that one would expect to see the condition more commonly than it is actually seen if this were the sole or major factor.

Of more significance is the fact that nearly all these infants have suffered from some other grave condition, such as sepsis,²⁴ pneumonia,²² diarrhea⁴⁸ (Case 3), intestinal obstruction⁴⁶ (Case 2), or congenital heart disease (Case 1). This would suggest that sclerema is secondary to another illness² and that the factor which causes it is common to all these illnesses. Signs of this factor, i.e., dehydration, low body temperature, and weakness, have been frequently observed. To these, we can add acidosis as still another concomitant. For the one state that all these infants had in common was shock, and from evidence in one of our patients (Case 3), the significant feature of shock in this condition is the insufficiency of peripheral circulation presumably due to vasoconstriction. This circulatory collapse may bring about such a reduction of peripheral temperature as to enhance fat-hardening.

Yet this explanation alone does not seem to account for the whole syndrome. The condition can be present at birth in the absence of exceptional trauma,⁶³ and scleremic infants seem unusually predisposed to develop debilitating illnesses which precede or are concomitant with the process. There is still the thickening of connective tissue bands^{26, 36, 47, 64, 65} (Case 2) to be explained. Two authors^{37, 38} considered this change to be of primary significance in the disease and minimized the role of fat change, if any, in this condition. The regularity of its presence in carefully prepared sections suggests that it is a significant mechanism in the induration of subcutaneous tissue. Since it occurs whether the fat cells are atrophied, normal, or engorged, the idea formerly entertained²² that the thickening is a manifestation of shrinkage has been discarded. There seems little doubt that this thickening represents a significant alteration of collagen. Recent work with thiouracil⁶⁶ may be of significance. Adults made temporarily hypothyroid with thiouracil develop "early scleroderma-like changes" with complaint of being "tight-skinned" and "muscle bound." Biopsy shows swelling of collagen fibers of connective tissue bands similar to that seen in sclerema. At the same time, the usual clinical picture of myxedema is lacking.

This does not signify, however, that changes were necessarily due to artificially induced hypothyroidism, but possibly that thiouracil may have had some unique effect of its own on connective tissue cells, possibly in selectively suppressing their metabolism. Several scleremic infants treated with thyroid^{23, 67} have recovered, but there is no evidence that these infants were hypothyroid. Hypothyroidism should not be present in the first few days of life if the mother were not obviously myxedematous, and these infants also showed no other signs of hypothyroidism either at the time or after recovery. The therapy may have had some influence on connective tissue cell metabolism, but the efficacy of thyroid has not been proved as other infants^{45, 47, 50} (Case 3) have recovered without its use. Reports of success with its use in infants who have poor temperature control, increased blood lipids, and a peculiar state of subcutaneous tissue are, however, provocative.

Two other possible etiologies should be discussed: infection and trauma. There is no question that these are important factors in subcutaneous fat necrosis, but on the bases of case histories and pathologic sections their possible roles in

typical sclerema seem unlikely. In the twenty-eight case reports of typical sclerema, only two (Hodder⁴⁶ and Case 2) mention unusual trauma at birth or afterwards. In ten cases^{23, 26, 37, 48, 64, 65, 68, 69} (Cases 2 and 3) where microscopic sections were examined, none showed evidence of traumatic necrosis of fat cells. Simple atrophy of cells has been reported in four instances.^{26, 48, 67, 69} As for infection, none of these sections showed evidence of cellular infiltration which should be present if local inflammation were to be a factor.

With respect to therapy, it is likely that heat of a degree sufficient to liquefy solidified fat (106° to 109° F.) applied externally to an infant in shock would probably increase damage to already injured vessels.⁷⁰ Its use is, therefore, possibly contraindicated. In addition to the possible salutary effects of thyroid, measures aimed at correcting the shock itself, i.e., the correction of dehydration, acidosis, and their complications,⁷¹ as well as the treatment of the primary condition may significantly improve sclerema. Many other treatments^{46, 49, 63} have been suggested but have probably not significantly altered the course of the disease.

SUMMARY AND CONCLUSIONS

Review of all available literature on sclerema and the reports of three additional cases here show that sclerema neonatorum is a definite entity clearly differentiated from subcutaneous fat necrosis and edematous states in the newborn infant. Histopathologic findings showed that thickening of connective tissue bands was the only significantly constant finding. By means of the Nile blue stain, the subcutaneous fat was found to react as neutral fat.

Various etiological theories have been proposed. Most of the evidence favors the hypothesis that sclerema neonatorum may be a manifestation of severe shock in early infancy, and that the hardening of fat and thickening of collagen fibers in the subcutaneous tissues may result from insufficiency of peripheral circulation.

The peculiar composition of infant fat lends itself to hardening, while it is suggested that disturbances of cell metabolism as a result of peripheral circulatory failure may influence the change in collagen.

There is little to suggest that trauma, local inflammation, or simple chilling are major factors in the etiology of typical sclerema. Dehydration probably contributes to circulatory inadequacy by reducing the blood volume, but is probably not the primary etiological factor.

It is recommended that therapy be based on the correction of shock and the treatment of the primary disease. The use of thyroid extract has been suggested and warrants further trial. Local therapy seems to hold little promise.

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CLINICAL SIGNS AND DEVELOPMENT OF SURVIVORS OF KERNICTERUS DUE TO RH SENSITIZATION

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ONLY a few years have elapsed since Landsteiner and Wiener¹ discovered the Rh factor and Levine and his co-workers² realized the bearing of this important discovery on erythroblastosis fetalis. During this short period of time, several hundred publications on the Rh factor from the hematologic, clinical, and pathologic aspects have appeared in the literature. A review by Potter³ in 1944 discussed 140 papers dealing with this subject. Most of them are concerned with the pathogenesis of erythroblastosis, the clinical course and treatment during the stormy neonatal period, and anatomic findings in infants who expired within the first few days or weeks of life. Little is known so far about the further development of children who survive the relatively rare and mostly fatal complication of icterus gravis neonatorum, called kernicterus.

Icterus gravis neonatorum and kernicterus are not disease entities but only clinical syndromes. While many cases published with this diagnosis were probably due to Rh sensitization, review of the older literature proves that the severe jaundice and its cerebral sequelae were frequently caused from septic infections, as in the case of Cornelia de Lange.⁴

The occurrence of kernicterus is usually given as approximately 10 per cent of the cases of icterus gravis. Only Ford⁵ reports that destruction of certain parts of the central nervous system is found in about 40 per cent of all cases of severe jaundice of the newborn infant.

The neuropathologic picture of kernicterus was first described by Orth⁶ in 1857. The etiology of his case remains uncertain since no family history is given. The term kernicterus was coined by Schmorl⁷ in 1903. Schmorl published the autopsy findings in 120 newborn infants who had died of icterus gravis. In only six instances, which means in 5 per cent of these 120 cases, did he observe typical changes in the brain, which he described in detail. The structures most commonly impregnated with pigment were: the caudate, lenticulate, subthalamic, and dentate nuclei, the thalami, the mammillary bodies, the cornua ammonis, the nuclei of the cranial nerves, the olives, and even parts of the cerebellar cortex, as well as the anterior and posterior horns of the spinal cord. This typical localization of the destructive process in the brain fully explains the characteristic motor disturbances in the patients to be described.

Later investigators have confirmed Schmorl's findings and added some details concerning the character of the degenerative process that takes place in patients who survive the neonatal period. Burghard and Schleusing,⁸ who published the necropsy findings in an infant who died at 5 months of age, reported that the nuclei involved in the destructive process were not then pigmented.

The ganglion cells, however, were shrunken and showed loss of the tigroid substance, and numerous cells containing fat granules were found within the affected areas. Zimmerman and Yannet,⁹ who described in detail the neuropathologic picture in one of their patients who expired at 3 years of age, mention that at this late stage of the process, the changes in the brain closely resembled those described by the Vogts¹⁰ as "status dysmyelinisatus." Since the etiology of this disease has never been found and the clinical signs are very similar to those of our patients, the few cases published so far may have been of some of the rare survivors of kernicterus.

In the very extensive German literature on "icterus gravis neonatorum familiaris" during the first quarter of this century, there are more than twelve cases of kernicterus obviously due to erythroblastosis, verified by anatomic studies. I only mention those with interesting family histories, published by Beneke,¹¹ Pfannenstiel,¹² Ylppo,¹³ Thorling,¹⁴ and Hilgenberg.¹⁵ All these infants died during the acute stage within the first few days of life. At this early period of research, I summarized the concept of icterus gravis and kernicterus as follows:¹⁶ "The pathogenesis is still enigmatic, our therapeutic measures so far have been of no avail. However, from the familial occurrence we may assume that some hereditary factor plays an important part." In the light of our modern knowledge, these old family tragedies are classical examples of Rh sensitization.

In the United States, Zimmerman and Yannet¹⁷ published a detailed study on kernicterus with an excellent description of the acute stage as well as observations of cerebral sequelae in a few surviving patients.

Among their own four cases, only the family history of Case 1, in which death occurred on the eighth day, is characteristic of Rh sensitization. In Cases 2 and 3 the severe jaundice was obviously due to sepsis. In Case 4 the history is too incomplete to allow any conclusion as to the etiology.

Among the seven cases of survivors of kernicterus which Zimmerman and Yannet collected from the older literature, I found only the one published by Guthrie¹⁸ to fulfill the criteria of kernicterus due to erythroblastosis. In the remaining six cases reported by Hoffmann and Hausmann,¹⁹ Greenwald and Messer,²⁰ and Spiller,²¹ the etiology is uncertain or not indicative of Rh sensitization.

The clinical picture of kernicterus and its cerebral sequelae, as described by Zimmerman and Yannet, is in short the following: The infant usually appears to be normal at birth. Jaundice starts before the second day and becomes rapidly intense. Evidence of involvement of the central nervous system is frequently observed even during the first days or weeks of life. Death usually occurs on or before the fifth day. In the few surviving patients, the early appearance of increased muscle tone is soon followed by athetoid movements of the extremities and rather severe mental deficiency. In one case cerebellar ataxia was the dominating symptom.

Recently Yannet and Lieberman,^{22, 23} studying the population of a training school for feeble-minded patients, found three typical cases of kernicterus due to Rh sensitization and three other cases with insufficient family history, whose clinical symptoms were very suggestive of kernicterus.

During the last few years ten additional cases of survivors of kernicterus were reported by Leonard,²⁴ Docter,²⁵ and Stiller.²⁶ No clinical details are given by Docter on his five cases except the interesting observation that some patients who are spastic when jaundiced tend to improve as the jaundice subsides and as they grow older. Of the four children described by Stiller, the oldest is only 3 years old. In two of his patients at the age of 5 months, he observed paresis of the N. abducens. One of them also showed bilateral blindness.

Considering the rare occurrence of survivors of kernicterus due to Rh sensitization and the fact that only fourteen certain cases have been published so far in the American literature, I was fortunate to observe the following eight typical cases among the neurological treasures of the Dixon State Hospital.

CASE REPORTS

CASE 1—B. S. was born Aug. 19, 1935. One sister, born in 1931, was living, in good health, and bright mentally. There were no pregnancies or miscarriages after his birth. He was full term, delivery was normal, birth weight was 6 pounds, 13 ounces. There were no apparent injuries or defects at birth.

Neonatal Period—He developed generalized severe icterus on the second day. The stools and urine contained large amounts of bile. On the third day slight opisthotonus was noticed. Blood examination on the third day showed 25 million red cells and 74 per cent hemoglobin. When the child was 17 days old the red count was only 158 million and hemoglobin 35 per cent. Subcutaneous fluids and three blood transfusions from 25 to 55 c.c. each of his father's blood were administered. He was discharged from the hospital in fair condition on Oct. 3, 1935.

Further Development—At the age of 9½ months he was unable to sit alone or to hold up his head. The diagnosis was icterus gravis with aplastic anemia and evidence of kernicterus.

At one year of age he was seen at the Mayo Clinic. Marked spasticity was then present. Soon after, an operation was performed to correct the hyperadduction of both legs.

Observation at the Dixon State Hospital—

Findings on admission (March 3, 1937). General condition and nutrition good. Head small, flattened occiput, circumference 17½ inches. Operation scars on both thighs. Undescended testes. Incoordinated movements of all four extremities. Vision seems normal. Hearing is questionable. Unable to walk or talk. I. Q. 42. Classified as imbecile with congenital cerebral spastic infantile paralysis, which would indicate that he was still spastic at this time.

Findings on Aug. 18, 1941 at 6 years of age: Has the appearance of a 3 year old boy. Both testes descended. No spasms or paresis. This child is in continuous motion, with athetoid movements of his arms and legs, grimacing, and moving his eyes. It is impossible to examine his reflexes. He walks, or better tumbles around the crib holding to the crib sides in a strange jerky way. His nickname is "Jitterbug." He seems to see but his hearing is questionable. He is not yet trained to toilet habits and has to be fed. He does not yet talk but seems to have some understanding. He takes pleasure in pulling other children's hair or picking at them. Probable diagnosis—kernicterus.

Nov. 6, 1941. Learned to walk alone but falls frequently due to disturbance of balance.

Oct. 12, 1944. B. is getting strong and mischievous. His gait has much improved but there is still a definite disturbance of his balance.

March 13, 1947. His gait has further improved, the disturbance of balance is still noticeable, especially when he changes direction. He is still in almost continuous motion, grinning and grimacing, mischievous, unsteady, gets into everything. He learned to feed himself in a messy way, goes to the toilet, does not talk, follows simple commands if signs are made to him, but shows no reaction to sounds. Seems to be completely deaf. I. Q. 22. Physically well developed. Weight, 50 pounds.

Rh Determination.—Rh determination on the parents' blood on April 25, 1947, more than eleven years after the patient's birth, gave the following result: Mr. S.—Type O—Rh positive. Mrs. S.—Type O—Rh negative No blocking Rh antibody. Titrations (1:1) of direct Rh antibody.

Summary.—This is a typical case of kernicterus due to Rh sensitization with severe jaundice and severe anemia of the newborn infant. There is serious retardation of his physical and mental development. He had one convulsion during the first year of life in the course of a respiratory infection. He was definitely spastic at one year of age, when an operation was performed to correct the hyperadduction of both legs. Athetoid movements are first mentioned at 18 months. At 6 years of age the spasms had completely disappeared. Especially interesting additional symptoms are severe disturbance of balance and deafness. He learned to walk alone at 6 years, three months of age. His gait improved gradually, and at the age of 11½ years the disturbance of his balance is noticeable only when he changes direction. He is physically well developed now. His I. Q. decreased from 42 at 1½ to 22 at 11½ years.

Case 2—G. L. was a full term infant, delivered by cesarean section on Dec. 31, 1939. Birth weight was 3,055 Gm. He was third in order of birth.

Mother's Obstetrical History.—The first child, a boy, was born in 1934 and was healthy and mentally normal. The second pregnancy was prematurely terminated at eight months' gestation by cesarean section, because the mother had eclampsia. The baby died soon after birth.

With the third pregnancy (G. L.) the mother was anemic and had again a moderate hypertension. Her blood was found to be Rh negative. The placenta showed the typical characteristics of erythroblastosis.

Neonatal Period.—Jaundice of the baby was noticed right after delivery. He had only 3.1 million red cells and 11 Gm hemoglobin. There were 115,000 nucleated red blood cells and erythroblasts. The child was treated with intravenous and intramuscular citrated blood transfusions. He was discharged from the hospital when he was 5 weeks old, his jaundice clearing. He weighed 3,160 Gm.

Further Development.—The jaundice lasted more than seven weeks. At the age of 2½ months he had the first convulsion; later he had mild convulsions up to 9 months of age. At 3½ months a diagnosis of cerebral spastic infantile paralysis and kernicterus was made by Dr. Buchanan. He was cranky and fretful during the first year, but had a happy disposition later. He had frequent attacks of high fever with colds or pneumonia. He also was a serious feeding problem. He learned to sit at 18 months. At the age of 2 years, 3 months an alternating convergent strabismus and mental retardation were noticed. At the age of 3½ years he was again found to have a moderate anemia. A pneumoencephalogram was made and reported to be normal. He could not yet stand or walk. He had generalized athetosis and some evidence of universal spasticity. He had a marked bilateral spastic squint. He apparently understood simple commands and there was no evidence of deafness.

Observation at the Dixon State Hospital—

Findings on admission (Dec. 5, 1943).—Fairly well developed. Circumference of head 10¼ inches; head symmetric and of normal shape. Convergent strabismus of both eyes; follows objects. Plays with toys. Both testes descended. All four extremities hypotonic; almost continuous athetoid movements of both arms, to a lesser degree also of his legs. Knee jerks normal on left side, questionable on right side. Abdominal reflexes positive. Sits alone; stands when holding to crib side. Makes incoordinated movements of his arms when trying to walk with assistance. Does not talk but seems to have some understanding and follows simple commands. Wets and soils himself, and has to be fed. I. Q. 14.

April 13, 1947: Weight 39 pounds. Height 41 inches. Circumference of head 20 inches. Convergent strabismus of both eyes and levoversion of right eye. Fundus of both eyes is normal. Follows objects, grabs them and plays with them. Vision and hearing seem to be normal. Is still in almost continuous motion with athetoid movements of both arms.

and legs, and grimacing. He walks around in the dormitory in a fast, excited way, holding to the crib sides, his right foot in planovalgus position, his left foot in varus position. Mild degree of lead pipe rigidity of both arms and legs, but is not hypertonic or spastic. Tendon reflexes increased. Babinski negative. Abdominal reflexes questionable. Does not yet talk. Cannot feed himself by spoon due to his incoordinated movements, but eats bread or cookies alone. He is partly trained to toilet habits. Has a happy disposition and likes to play with other children. His I. Q. was found to be only 12, which may be a little too low.

Oct. 8, 1947: Learned to feed himself by spoon. Walks more steadily and has a better understanding.

Summary.—This is a case of typical kernicterus due to erythroblastosis with jaundice starting right after delivery and lasting over seven weeks. There was moderate anemia during the neonatal period. There were frequent convulsions from 2½ to 9 months of age. He was a serious feeding problem and had frequent attacks of high fever. At 3½ months he was definitely spastic. At 3½ years there was only a mild degree of spasticity, but there was generalized athetosis. At 5 years of age he had periods of hypotonia. He sits alone and stands when holding the crib side. At 7 years his spasticity disappeared; we find only a mild degree of lead pipe rigidity of all four extremities, which increases with intentional movements. He walks around the cribs. He just learned to feed himself by spoon. He tries hard to talk and has some understanding; he asks for the toilet by signs. He has a happy disposition. His I. Q. is given as only 12.

CASE 3.—T. M. was born on May 29, 1943. He was full term and delivery was normal. No instruments were used. He was third in order of birth. He weighed 7 pounds, 14 ounces.

Mother's Obstetrical History.—The first child was a healthy normal boy, the second child, a healthy normal girl.

The third child was our patient, T.

The fourth pregnancy was a stillbirth of seven months' gestation with congenital malformations, without feet, and born in September, 1944. During this last pregnancy the mother developed a severe toxemia with generalized edema, high blood pressure, and transitory mental disturbance.

Rh Determination on the Family.—The mother and the second child are Rh negative. The father and all the other children are Rh positive. This would indicate that the father is heterozygote (recessive), Rh positive.

Neonatal Period.—T. was already jaundiced at birth. His jaundice became progressively worse. On the third day he started to vomit frequently and cried almost continuously. From the third to the sixth day the following spells were observed: The entire body seemed to jerk, then suddenly the baby gave out a loud cry and became very rigid for a few minutes. On the fifth day he was given 10 c.c. of whole blood with 40 c.c. of normal saline. On the sixth day the red blood count was 4.34 million and hemoglobin 87 per cent. By the seventh day he retained his feedings but seemed very listless most of the time and cried only when touched or moved. When 11 days old his condition was unchanged, and he was transferred to the Children's Memorial Hospital. On admission there he was found markedly jaundiced; his icteric index was 194. His spleen was palpable, his liver enlarged, reaching to the level of the umbilicus in the nipple line. He had a moderate anemia, 2.75 million erythrocytes and 104 Gm hemoglobin. On the thirteenth day 75 c.c. of Rh negative blood were given. Following this transfusion the red count rose to 4 million and the hemoglobin to 14.8 Gm. The baby left the hospital apparently in good condition on July 6, 1943 with an icteric index of 18.

Further Development.—According to reports of the very intelligent mother, the patient was very rigid and hard to handle after returning home. For four months he was subject to projectile vomiting. He was very fussy and cross during this time and slept only for short periods. At the age of 6 months he quieted down somewhat. During a period of observation at the Children's Memorial Hospital at 5 months of age, he showed signs of spasticity, nervous irritability, and mental retardation. He also had a tendency to develop extremely high temperatures, as high as 105° F. during pneumonia in May, 1944.

Observation at the Dixon State Hospital.—

Findings on admission (October, 1944): Underdeveloped for his age. Weight 21 pounds. Height 30 inches. Head and face asymmetric, convex to left side. Fontanel open. Circumference of head 19 inches. Big, slightly deformed ears and high, narrow palate. Genitals normal. Does not focus objects nor grab them. His pupils do not react to light. His vision is questionable. Both arms are hypertonic, his legs show increased tendon reflexes, more pronounced on left side. No Babinski. Athetoid movements of his fingers; he does not even grasp objects which are placed in his hands. He cannot sit or hold his head up. I. Q. 31.

March 27, 1947: Weight 30 pounds. Good general condition. Head flattened on back, circumference 20 inches. Fontanels closed. Mild, alternating squint of both eyes, horizontal nystagmus at times. Pupils react to light. His fundi are normal. He follows objects with his eyes, tries to grab them with incoordinated movements and holds them when put into his hands. He tries to play with a rattle or cloth toy, but always loses hold due to his exaggerated atactic movements. Normal reaction to sounds. Rigidity of both arms, while his legs are hypotonic and mostly spread in a froglike position. His knee jerks are not increased. No clonus or Babinski. At times he stretches his legs out in a jerky movement, spreading his toes. Frequent athetoid movements of his arms and hands. Cannot hold his head up or sit. No feeding problem. Seems to know the girl who takes care of him. Smiles when given attention. Does not talk nor seem to have any understanding. I. Q. only 10.

Summary.—This is another case of typical kernicterus due to Rh sensitization. The child was already jaundiced at birth. Signs of cerebral involvement started on the third day. In spite of severe jaundice with an icteric index of 194 and marked enlargement of the liver, he developed only a moderate degree of anemia. The hyperpyrexia would indicate involvement of the hypothalamic region. Interesting is the change in his legs from spasticity with increased tendon reflexes to hypotonia, and, also, his transitory blindness. The lack of reaction of his pupils to light is due to a lesion in the quadrigeminal plate. There was almost no mental progress during the past two years, which accounts for the drop in his I. Q. from 31 down to only 10.

CASE 4.—E. P. was born on June 10, 1943. A cesarean section at eight and one-half months' gestation was performed because of narrow pelvis. The birth weight was 7 pounds, 3½ ounces. The mother's health during pregnancy was good.

Mother's Obstetrical History.—The first child, born in 1932, was a healthy bright boy. The second child was a Mongolian idiot, born in 1938. He died of scarlet fever at the age of 2 years, 9 months. The third pregnancy resulted in a miscarriage in the spring of 1942.

The fourth child was our patient, E., born in 1943.

Rh Determination in 1944 on the Family.—The mother's blood was Rh negative, the father's and E.'s blood were Rh positive.

Neonatal Period.—All we know is that E. developed severe jaundice right after birth.

Further Development.—At 13 months of age he spent four weeks for observation at the Cook County Hospital. At this time he was unable to sit up and had a red blood count of 4.34 million. No other findings were reported. The diagnosis was: cerebral agenesis.

Observation at Dixon State Hospital.—

Findings on admission (Jan. 12, 1945): Weight 20 pounds. Height 33 inches. Under-sized for his age. Shape of head slightly scaphocephalic; circumference 18¼ inches. Fontanels closed. Ears slightly deformed. High, narrow palate with protruding upper gums. Only left testicle descended. Arms mostly bent upward and hands clenched to fists. Legs hypertonic, lead-pipe spasticity. Knee jerks increased. No clonus or Babinski. Holds up his head; cannot sit alone but stands on tiptoe and even tries to take some steps when supported. He follows objects with his eyes but does not grasp them. He has a mild left internal strabismus. He seems to hear. He smiles when given attention. He does not talk or seem to understand. All his movements are incoordinated.

May 31, 1946: E. pulled himself up to stand in bed for the first time, holding to his crib side. His movements are still incoordinated.

Aug. 15, 1946: He learned to move around in a walker and enjoys this very much.

April 5, 1947: At three years, 10 months of age his weight is only 24 pounds. Well proportioned body, good muscles. He tries to talk (jabber-) and seems to understand. He knows people who take care of him. When he sees the writer coming, he stands up, smiles, gets very excited, and reaches for a cookie or wants to be petted. He plays with plain toys, changing them from one hand to the other and looking at them from all sides without putting them in his mouth. He tries to feed himself with his fingers since his movements are still too incoordinated to use the spoon. He has just started to be toilet trained. He stands and walks tiptoe when holding to the crib side with fast, jerky, excited movements. He enjoys walking very much. Both testicles are descended now. He still shows marked lead-pipe spasticity of all four extremities, more pronounced in his arms. Spontaneous Babinski of his left foot. He sees and hears. No more squint. Coordinated eye movements. Very happy disposition. His I. Q., which was 25 on admission, was only 17 on April 15, 1947, which may, however, be too low.

Summary.—This is another case of typical kernicterus due to Rh sensitization. Marked lead pipe spasticity is still present at nearly 4 years of age. His gait is spastic on tiptoe. The spontaneous Babinski reflex indicates involvement of the pyramidal tracts. His movements are incoordinated, but he does not exhibit the continuous athetosis and grimacing which characterize some of the other patients. There is transitory strabismus of the left eye. Notwithstanding the very early appearance of his jaundice, this child seems brighter than most of the other patients.

CASES 5 AND 6—W. A. and M. A.

Mother's Obstetrical History.—The first child was a normal bright boy, born in 1935.

The second child was W. A., born June 10, 1938 at full term, weighing 6 pounds, 7 ounces. He had severe jaundice soon after birth. Blood transfusions were given. Mental retardation was already noticed at 3 months of age. He was admitted to the Dixon State Hospital at the age of 13 months, where he died two months later of dysentery and bronchopneumonia. He was unable to sit up or to hold up his head. He showed incoordinated movements of all four extremities, especially of his right leg. His vision and hearing seemed to be normal. His I. Q. was given as 38.

The third child was M. A., born Aug. 1, 1944 at full term, after an easy delivery. He weighed 5 pounds, 13 ounces. There were no miscarriages, premature births, or stillbirths after M. The mother's health during both pregnancies was only fair. She was very nervous and vomited throughout the nine months.

Rh Determination—This showed the mother to be Rh negative, the father and M. to be Rh positive.

Neonatal Period.—M. appeared to be normal at birth but looked yellow as a lemon only six hours after delivery. He also developed a high fever. By the fifth day the baby was deeply jaundiced, had a cerebral cry, a large, palpable spleen, a bulging fontanel, and marked anemia, typical of erythroblastosis. He was given 75 c.c. of Rh negative blood on two consecutive days after which his blood picture improved.

Further Development—At 3 months of age he was reported to have repeated "salaam spasms" and to present a picture of intracranial damage. At 5 months he had pneumonia. At 8 months of age the court psychiatrist described him as a "flabby infant," quite uninterested. He could not sit up, his eyes followed objects poorly, and he did not reach for them. He was mentally retarded and weighed 13 pounds, 2 ounces. The mother reported that he slept during the day and stayed awake nights.

Observation at the Dixon State Hospital.—

Findings on admission (May 17, 1945): 9½ months old. Weight 14½ pounds. Height 27 inches. Head deformed, flattened on back. Circumference 16½ inches. Forehead deformed. Convergent strabismus of right eye; pupils react to light. The muscles of his lower extremities are weak, but he kicks with his legs. Knee jerks normal. Babinski positive. I. Q. 44.

April 5, 1947: At the age of 2 years, 8 months this child weighs only 20 pounds. His head is still asymmetric, protruding on right side and flattened on back. Circumference 18½ inches. Fontanels closed. Right ear larger than left ear, slightly deformed and protruding. Eyes normal. No strabismus any more. Well proportioned body. He follows objects and grabs them with coordinated movements of both arms. He changes objects from one hand to the other, playing with them without putting them into his mouth. Small scrotum; testicles undescended. Normal tonus and reflexes on his arms. His legs at times show a mild degree of lead-pipe rigidity. His feet are mostly in varus position. Knee jerks increased, no Babinski. No athetoid movements! Holds up his head. Cannot sit without support. Smiles, likes attention. Takes his feedings well. Does not yet try to talk or seem to understand. His present I. Q. is only 19 as compared to 44 on admission.

Nov. 9, 1947: Learned to sit alone and to stand for moments holding to crib side. Legs are mostly hypotonic. Seems to be definitely hard of hearing.

Summary.—These two brothers had the typical history and signs of kernicterus due to Rh sensitization. W. died at 15 months of age after only a short period of observation. It is of special interest that M., in contradistinction to all the other patients with kernicterus, was never spastic and has no athetoid movements so far. Tonus, reflexes, and coordination of his upper extremities are perfectly normal. Only his legs exhibit a mild degree of lead-pipe spasticity. He had a transitory strabismus of his right eye and is definitely hard of hearing. His intelligence is higher than that of several other patients, in spite of the very early onset of his jaundice and the relatively late treatment. Furthermore, he is the only patient in whom a bulging fontanel during the first days of life was reported.

CASE 7.—L. W. was born March 21, 1945 after eight months' gestation and normal delivery. His birth weight was 5 pounds, 8 ounces. The mother's health during pregnancy was good.

Mother's Obstetrical History.—The first child, a boy, was born three months prematurely in December, 1938, and died a few hours after birth. The cause of the miscarriage was unknown.

The second child was a boy, born at full term, with normal delivery, in September, 1940. His subsequent development was normal. He is healthy and bright mentally. The third child was a boy, full term, with normal delivery, in May, 1943. No details are known concerning his neonatal period. He had a perfectly normal development. He died in March, 1944 of encephalomeningitis due to *Streptococcus viridans* infection.

The fourth child was our patient, L. W.

Rh Determination on the Family.—This showed the mother and the normal second boy to be Rh negative, the father and L., Rh positive.

Neonatal Period.—L. was listless from birth. Jaundice was first noticed on the third day, at which time his face became puffy and his temperature rose to 102° F. Subcutaneous fluids were given. On the fifth day the infant had developed general spasticity with retraction of his head. The jaundice was more intense. On the sixth day he was given 40 c.c. type specific Rh negative blood intravenously. On the tenth day his jaundice was already less pronounced. He was discharged home at the age of 2 weeks, still spastic. Between his sixth and fifteenth days, ten blood examinations were performed. They showed that he developed only a moderate degree of anemia; the lowest point was reached on his sixth day with 3.6 million red blood cells and 9.5 Gm. hemoglobin. On his ninth day he already had 5.2 million red blood cells and 17.5 Gm. hemoglobin. He never showed any increased number of normoblasts or erythroblasts.

Further Development.—At 9 months of age he was seen by Dr. Buchanan, who states the following diagnosis: Neurological evidence of kernicterus. Increased deep reflexes and marked spasticity in all four limbs. Very limited in understanding mentally.

Observation at the Dixon State Hospital—

Findings on admission (Feb. 4, 1946): At the age of 10½ months, weight 18 pounds, height 29½ inches. Head and face asymmetric, convex to left side. Fontanel one finger-breadth open. Circumference of head 17 inches, biparietal diameter only 4½ inches. Left

ear enlarged, misshapen, and protruding. High, narrow palate. Pupils wide, reaction to light questionable, does not follow objects; horizontal nystagmus to the left side and head mostly turned to the left side. Seems to be blind and also shows no reaction to sound. Frequent jerking of arms and legs. Temporary rigidity alternates with periods of relaxation. Increased deep tendon reflexes of both arms and legs, most pronounced of his left leg. No clonus or Babinski. Cannot sit up or hold up his head. I. Q. 15.

During the entire period of observation at our Children's Hospital, this patient was running high temperatures of remittent type, frequently up to 101° or 105° F., probably due to the still active process in his brain. He was under continuous penicillin medication which, obviously, was of no avail. From February 18 to Feb. 23, 1946 he had bronchopneumonia; from March 14 to March 16, 1946 he had a very mild case of mitigated measles (convalescent serum given two days after exposure). On March 25, 1946 he developed another bronchopneumonia, his temperature rapidly rising to 108.4° F. He expired thirty-six hours later without any signs of meningitis.

Autopsy Findings: Old and fresh bronchopneumonia. The brain weighs 800 Gm. There is thick, gelatinous edema of the meninges. Both lateral ventricles are moderately dilated. Microgyria of both occipital lobes was found. The brain was sent for microscopic examination to Dr. Lichtenstein, Neuropsychiatric Institute, Chicago, from whom we have received no report as yet.

Summary.—This was a case of typical kernicterus due to Rh sensitization in a patient who expired at one year of age while the process in his brain was still active. Especially interesting features in this case are the hyperthermia and the combination of deafness and blindness. Striking is the fact that this patient, who exhibited severe damage to his brain, had only a moderate degree of jaundice and anemia during his neonatal period.

CASE S.—M. K. was born Nov. 25, 1942, at full term; labor was dry and long, but no instruments nor anesthetics were used. Birth weight was 7½ pounds. No peculiarities were noted at birth.

Mother's Obstetrical History.—The first child was a healthy, normal girl. There were no miscarriages or premature deliveries. After her first delivery the mother had a severe hemorrhage and received an intravenous transfusion of one pint of plasma and one pint of whole blood.

The second child was our patient, M. K.

Rh Determination.—In 1945 the mother was found to be Rh negative, the father and patient to be Rh positive.

Neonatal Period.—M. became jaundiced on the second day and developed a moderate degree of anemia. On the seventh day the red blood count was 3.4 million, the hemoglobin was 62 per cent, there was only 1 per cent normoblasts. At four weeks of age the red blood count was 3.06 million, the hemoglobin was 56 per cent. She was treated with repeated small blood transfusions. The patient did not reveal any cerebral signs except a moderate sluggishness. She was discharged from the hospital after six weeks, still jaundiced, weighing 8 pounds.

Further Development.—According to the report of the very intelligent mother, some yellow tinge of her skin and eyes could be noticed up to 4 months of age! M. was a very quiet baby. She never cried, took her feedings well, did not vomit, and never had convulsions. At the age of 6 months she did not yet hold up her head and did not show any interest in her surroundings. Only at 3 years of age did she learn to sit alone. About the same time she started her queer athetoid movements. Her arms and legs were very flabby. When the mother tried to have her stand her legs just gave in; there was no resistance at all. Only when she became excited did she stiffen herself. When Dr. Buchanan examined her at 2½ and 3½ years of age he stated the diagnosis of spastic quadriplegia with choreoathetosis due to kernicterus after erythroblastosis.

Observation at the Dixon State Hospital.—

Findings soon after admission on Sept. 5, 1947: Four years, 9 months of age. Pale; nutrition fair. Both arms and legs are markedly hypotonic; there is no resistance to passive

TABLE I. IMPORTANT DATA IN EIGHT CASES OF KERNICTERUS, DUE TO RH SENSITIZATION

NO. OF CASE	ORDER OF BIRTH AND TIME OF GESTATION	ONSET, DEGREE, AND DURATION OF JAUNDICE	DEGREE OF NEONATAL ANEMIA	ONSET OF CEREBRAL SYMPTOMS	ONSET AND METHOD OF TREATMENT	CEREBRAL SEQUELAE OF KERNICTERUS AND FURTHER DEVELOPMENT
1. B. S.	Second pregnancy Full term	Second day, severe, duration unknown	Severe: RBC 1.58 million, Hb. 35% on 17th day	Third day opisthotonus	3 blood transfusions, 50 c.c. father's blood	First spastic, later bilateral athetosis, grimacing, severe disturbance of balance, deafness, I. Q. 42-22
2. G. L.	Third pregnancy Full term	Right after delivery, severe, over 7 weeks	Moderate: RBC 3.1 million, Hb. 11 Gm. first day	3rd month convulsions, 4th month spasticity	Transfusions of citrated blood started 1st or 2nd day	First spastic, later general athetosis, grimacing, periods of hypotonia, convergent strabismus, I. Q. 14
3. T. M.	Third pregnancy Full term	Present at birth, severe, 5½ weeks	Moderately severe: RBC 2.75 mil. Hb. 10.4 Gm. 11th day	3rd day rigidity, jerking, cerebral cry, vomiting	75 c.c. of Rh-neg. blood on 13th day	Projectile vomiting, insomnia. Hyperpyrexia, first spastic, later hypotonia and athetosis, transitory blindness, alternating squint, I. Q. 31-10
4. E. P.	Fourth pregnancy 8½ months	Around third day severe, duration?	Unknown	Unknown	None	Marked lead-pipe spasticity athetosis, ataxia, strabismus, I. Q. 25-17
5. W. A.	Second pregnancy Full term	Soon after birth, severe, duration?	Unknown	Unknown	Unknown	Incoordinated movements, unable to sit or hold up his head, I. Q. 38
6. M. A.	Third pregnancy Full term	6 hours after birth, severe, duration?	Moderately severe on 5th day	5th day cerebral cry, 3 months spasms	2 transfusions, 75 c.c. Rh-neg. blood on 5th and 6th days	Mild degree lead-pipe rigidity of legs, no athetosis nor ataxia of arms, transitory strabismus, hard of hearing, I. Q. 44-19
7. L. W.	Fourth pregnancy 8 months	Third day, severe, 2-3 weeks	Moderate: RBC 3.6 million, Hb. 9.5 Gm.	Listless from birth, general spasticity 5th day	40 c.c. type-specific Rh-neg. blood on 6th day	Hyperthermia, blind and deaf, rigidity and frequent jerks alternating with relaxation, I. Q. 15
8. E. K.	Second pregnancy Full term	Second day, severe, 4 months	Moderate: RBC 3.4 million, Hb. 62% on 7th day	Unknown	Repeated small blood transfusions	Atonic diplegia with generalized athetosis and deafness, I. Q. 18

movements! Knee jerks cannot be elicited, but spontaneous and reflex Babinski are present. Abdominal reflexes positive. Coordinated eye movements, no squint. She follows objects with her eyes and grabs them with mild degree of ataxia. She is in almost continuous motion with slow athetoid movements of her extremities, and grimacing. She shows no reaction to sounds, not even to loud noises, and appears to be completely deaf. She follows simple commands when signs are made to her. She sits alone and just learned to walk with exaggerated movements when holding to crib-side. She tries to feed herself, does not talk, and still wets and soils herself. Her I. Q. is given as only 18, which may be partly due to the fact that the examiner did not realize this child was deaf.

Summary.—This is a typical case of kernicterus due to Rh sensitization with unusually long-lasting jaundice and only mild anemia. There were no signs indicative of involvement of the central nervous system during the neonatal period and up to 3 years of age, except that the child was very quiet and her muscles were very flabby. At 3 years of age athetoid movements were first noticed. She is now 5 years old and exhibits the picture of atonic diplegia with athetosis, complete deafness, and severe mental retardation.

COMMENT AND CONCLUSIONS

After a short review of the literature, with special reference to the pathogenesis and neurological signs of kernicterus, eight cases observed at the Dixon State Hospital are described in which the diagnosis of kernicterus due to Rh sensitization was established. The development of these children was followed for several years, the oldest of them now being 11½ years of age. These cases fall clinically into four distinct groups: In the first there is generalized athetosis due to destruction in the corpus striatum and globus pallidus. In the second there is persistent spasticity from involvement of the pyramidal and extrapyramidal systems. In the third, ataxia and disturbance of balance are the predominant features suggesting cerebellar degeneration. In the fourth, atonic diplegia from involvement of the extrapyramidal tract dominates the picture. Most patients, of course, show combinations of signs of all these four varieties. Interesting is the change, in some of our cases, from spasticity to hypotonia.

In addition to these motor disturbances, which have already been observed by Yannet and Lieberman, a considerable percentage of our patients exhibit cranial nerve signs which, to my knowledge, have not been described before in survivors of kernicterus. Four patients are deaf; one of them, who, however, died at one year of age, was blind and deaf; another had a transitory blindness. Several patients had eye signs suggestive of transitory or permanent involvement of the third or sixth cranial nerve nuclei.

The mental development in most of our cases was markedly retarded from the beginning and soon came to a standstill. This would account for the rapid decrease in the intelligence quotient with increasing age.

As to the pathogenesis of the special syndrome of kernicterus, our cases confirm the observations of previous authors, that there is no correlation between the degree of jaundice or anemia during the neonatal period and the occurrence or degree of cerebral damage. Our Cases 4 and 7 would indicate that not even a very early onset of the jaundice is necessary to produce severe destruction in the brain.

The part played by damage to the liver in the etiology of icterus gravis neonatorum is now generally recognized. The question is still open to discussion, however, as to why the destructive process has a predilection for the nuclear

masses of the brain. According to Langworthy,²⁷ the process of myelination does not start in these structures before the twenty-eighth week of gestation and is not completed until the fourth month after birth. This would mean that these regions of the brain are in a stage of rapid development and, therefore, of lower resistance at the critical time when toxic substances due to anaphylactic reactions or insufficiency of the liver are circulating in the blood of erythroblastotic infants. Our neurologists will have to find if these nuclei show increased tendency to absorb pigment during later life.

There is another problem, to the solution of which our material seems to furnish a valuable contribution. How shall we explain that involvement of the brain occurs only in a certain percentage of the cases of malignant jaundice of the newborn infant? May we, in addition to the Rh allergy of the mother, find another constitutional hereditary factor predisposing the fetal brain to damage?

There are families in which the nervous system of the members seems to be abnormally susceptible to damage from infections and toxic or emotional disturbances. These are the families whose children may become victims of poliomyelitis or spinal meningitis during an epidemic or develop convulsions in the course of infections with high fever. The adults are frequently very intelligent but have high-strung personalities.

From my own experience I remember three siblings who developed serous meningitis in the course of respiratory infections; two brothers suffering from the rare bulbar type of poliomyelitis; and three siblings, of whom one was a Mongolian imbecile, the second developed encephalitis after diphtheria toxoid immunization, and the third developed spinal muscular dystrophy.

In the family history published by Beneke,¹¹ three children out of five died in convulsions. In Pfannenstiel's¹² family there were two typical cases of kernicterus among three children with fatal icterus gravis. Thorling¹⁴ reports four fatal cases of erythroblastosis in one family, three of whom had cerebral symptoms. In the family described by Zimmerman and Yannet,¹⁷ the first child had hydrocephalus with spina bifida and died in convulsions on the fifth day. The following three children developed icterus gravis, and two of them died with typical symptoms of kernicterus.

Reviewing the family histories of our eight cases under this aspect we find the following: In Case 2 the mother had eclamptic convulsions during a previous pregnancy. The patient himself had frequent convulsions up to 9 months of age. In Case 3 the father, a highly intelligent man, developed a severe depression after realizing his child was abnormal. The mother, in the course of her following pregnancy, developed a nervous breakdown with transitory mental disturbance when she felt she was carrying another abnormal child. In Case 4 one of the siblings was a Mongolian idiot; the mother is a very intelligent but highly strung person. Cases 5 and 6 were two brothers, both suffering from kernicterus. Their mother is a very nervous person, who vomited throughout the entire nine months of both pregnancies and who calls herself a "nervous wreck." In Case 7 one brother died of encephalomeningitis due to *Str. viridans* infection. Further studies will be necessary to support this constitutional hypothesis.

PULMONARY CALCIFICATION IN TWINS

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PULMONARY calcifications in childhood have long been of interest to the pediatrician, the public health officer, and the radiologist mainly for the diagnostic possibilities, the treatment, advice, and prognosis that may be offered the patient. In the past, miliary calcification of the lung was thought to be due primarily to tuberculosis. In recent years, other diseases have been given more consideration as causes of such calcification.

It is not the purpose of this paper to describe in detail the differential diagnosis of pulmonary calcification in childhood but to present two cases of calcification occurring in twins and to discuss a disease which simulates miliary tuberculosis and may be a probable diagnosis in these cases. The etiological agent has never been identified in either case.

CASE REPORTS.

CASE 1.—The patient was a 10-year-old white female. She was born in Omaha, Nebraska. She was adopted and lived there until 10 months of age, at which time she moved to Denver, Colorado. When she was 3 years old, her parents moved to Chicago and she stayed there for a month. Her next residence was Fort Riley, Kansas, and during her stay at this post, she took a two-month trip to California. In 1945 she moved to Battle Creek, Michigan, where she has since resided.

Past History.—In infancy she had many colds, and a chest plate taken at 10 months of age revealed "one tiny spot in the lung." While at Denver she was well, but in Chicago she had many "asthmatic attacks," which were aided by adrenalin. The asthmatic condition disappeared after moving to Kansas. In June, 1946, while residing in Michigan, she visited Iowa. Here she was stricken with poliomyelitis and hospitalized for about five weeks.

She was seen in the dispensary at Percy Jones General Hospital for the first time in July, 1946, regarding her poliomyelitis. She was found to have weakness and atrophy of the left anterior tibial muscles, and physiotherapy was advised. In January, 1947, she was again seen because of a boil on the right buttock of one week's duration and a small lump in the right groin which had increased in size over a period of four months. It was also noticed by her mother that she had been having a low-grade remittent afternoon fever. There was no history of cough, chest pain, or night sweats, but she had anorexia with slight weight loss.

Physical Examination.—Examination at this time revealed a well-developed, pale, moderately thin child weighing 51 pounds. The eye, ear, nose, and throat examinations were essentially negative. Cardiac findings were negative. The lungs, to auscultation, revealed decreased breath sounds over the entire right lung field. No masses were palpable in the abdomen. There was a hard, tender, reddened area on the right buttock with two draining sinuses. In the right groin there was a nontender, freely movable mass about one centimeter in diameter. Examination of the extremities revealed atrophy and weakness of the left leg.

Laboratory Studies.—Laboratory studies at this time showed a red blood count of 4.1 million, hemoglobin 80 per cent, white blood count of 6,000, with a differential of 48 neutrophils, 42 lymphocytes, 7 monocytes, and 3 eosinophiles. The sedimentation rate was 6 mm. in one hour. The urine was essentially negative. The chest plate revealed many small areas of calcification in the right lung field, as shown in Fig. 1. A subsequent flat plate of

From the Outpatient Department, Percy Jones General Hospital, Battle Creek, Mich.

the abdomen and skull films were read as being negative. Tuberculin tests done with P.P.D. were negative in dilutions of 0.00002 mg., 0.0005 mg., and 0.005 mg. Histoplasmin skin test revealed a one plus reaction in forty eight hours to 1:100 dilution and a two plus reaction to 1:10 dilution in forty-eight hours. Coccidioidin skin tests were negative. Because the child continued to run a low-grade fever, did not gain weight, and the node in the right groin did not decrease in size, a biopsy of this node was done. The pathologic report was "reactive hyperplasia." Prior to this operation, further blood studies were done. The Kahn test was negative. Clotting time was ten minutes, bleeding time one minute and five seconds.

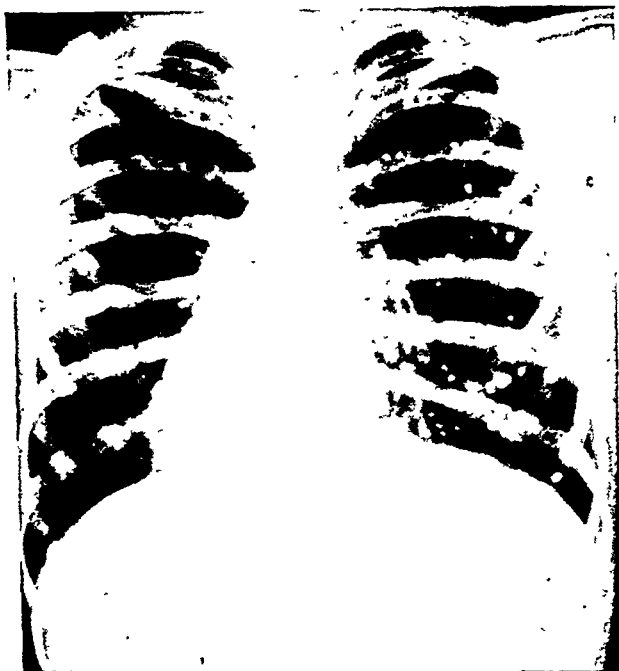


Fig. 1.—Case 1. Multiple calcifications seen in both lung fields, being more prominent on the right.

In April, 1947, a sternal aspiration was done which showed normal marrow with no parasites seen. The patient was not seen again until August, when she developed pyoderma of both feet. Culture revealed streptococcus and staphylococcus but no fungi. A repeat blood count at this time revealed a hemoglobin of 90 per cent, a red blood count of 4.4 million, and a white blood count of 6,200, with 38 neutrophils, 55 lymphocytes, 5 monocytes, 2 eosinophiles. In September, she complained of cough, sputum production, and remittent fever. Cultures and smears of the sputum failed to show tubercle bacilli or fungi, but long chains of streptococci were found. Physical examination revealed a well-developed, rather thin female weighing 50 pounds. There were no new physical findings except for small, nontender cervical and inguinal nodes bilaterally. Chest plates have been taken at intervals without any changes being observed in the lungs. No specific therapy has been given.

CASE 2.—The second patient is a twin sister of the girl whose case has just been described. She has traveled to the same places. They have always slept in the same bedroom but in separate beds. She has always been healthy except for pneumonia at 14 months of age and has never had frequent colds. She was brought to the dispensary at Percy Jones General Hospital for routine physical examination when her sister first became sick in January. Physical examination was essentially negative except for bilateral axillary and inguinal nodes. Tuberculin test was negative to all dilutions, and to histoplasmin she showed a

one plus reaction to both the 1:100 and 1:10 dilution. Coccidioidin skin test was negative. An x-ray of the lungs revealed a small area of calcification in the left lower lung field, as seen in Fig. 2. She was taller and weighed more than her sister. Since she has been asymptomatic, further studies have not been done.



Fig. 2.—Case 2. A single calcification seen in the left lower lung field.

DISCUSSION

The cause of the pulmonary calcification in these cases is not known. If the skin tests are of any significance, one must consider histoplasmosis or some other fungus infection as the possible etiological agent. Were Case 1 a nonfatal case of miliary tuberculosis which had calcified and not progressed, one would expect the tuberculin skin test to be positive. It is rare for a person who is once positive to a low dilution of tuberculin to become negative, though this is said to occur in the terminal stages of a fatal case or with an overwhelming infection. The same may also be said for histoplasmosis. The specificity of the histoplasmin skin test is doubtful. Palmer¹ studied 3,105 student nurses from various parts of the United States by means of the tuberculin and histoplasmin skin tests and x-rays. Of this group, 294 had pulmonary calcifications, with only 10.4 per cent reacting to the tuberculin; 31.1 per cent reacted to histoplasmin, and 34.1 per cent reacted to both. Only 1.2 per cent did not react to either. From this study he concluded that if the histoplasmin skin test is specific, histoplasmosis is the principal nontuberculous cause of pulmonary calcification. On the other hand, Emmons and his associates² do not think it is specific because they showed cross-reactions to occur in coccidioidomycosis, blastomycosis, and haplomycesis.

Smith⁴ also demonstrated that a cross-sensitivity exists between haplosporangium and coccidioidin. Christie and Peterson² studied 181 children. They found twice as many had calcifications as were tuberculin positive, and 73.5 per cent were histoplasmin positive.

Histoplasmosis is a world-wide disease and usually thought to be fatal. The etiological agent is the fungus *Histoplasma capsulatum*, with the reticuloendothelium the most involved element in the body. The course is variable, depending upon the severity of the infection. Many different symptoms may be manifested. Parsons and Zarafonitis,¹ in reviewing seventy-one cases in the literature, found that an irregular fever was an almost constant feature. The blood generally shows an anemia, with a normal to low white count, and with a possible increase of lymphocytes in the differential. The physical signs are also variable. Because the reticuloendothelium is most often involved, the spleen, liver, and lymph nodes are generally enlarged. However, any organ in the body may be involved. How the organism enters the body is not definitely known. It may enter through the skin, but the mouth is considered the most likely portal of entry since it is commonly affected, as are the pharynx, lungs, and gastrointestinal tract. The mode of transmission is not known. The dog is susceptible to the disease, and this may be a factor in its spread. McLeod and his associates⁵ reported four cases of histoplasmosis occurring in Virginia within a radius of eight miles. Two of these cases were in siblings. This may indicate that the disease is transmitted from one to another.

In the United States the disease is most prevalent along the eastern slope of the Mississippi River basin and the bordering states of the western slope. Whether there is a correlation between the incidence of the disease and the amount of farming done in these areas is not known. Parsons and Zarafonitis² showed that eleven of the seventy-one cases they reviewed were in children of less than one year of age. Below the age of 10, the incidence of the disease is the same in male and female. After one year of age there is a decrease in the number of cases, with a rise again at 40 years of age. At this age the male adult is infected more commonly than the female. This is also true of actinomycosis and coccidioidomycosis.

The diagnosis has not been made in many cases until autopsy. When trying to make a diagnosis of histoplasmosis, blood smears should be examined for the parasites. They are found in the polymorphonuclear and monocyte cells. If this does not reveal the parasites, bone marrow studies, biopsies, and stool, sputum, and urine cultures should be performed. Skin-testing with histoplasma and x-rays of the chest are also important in helping to make a diagnosis.

As stated previously, the symptoms of the disease are variable. This makes the differential diagnosis difficult. When pulmonary calcifications are found, other fungus infections should be considered. Cox and Smith⁷ and Aronson and his associates⁸ showed that coccidioidomycosis is responsible for pulmonary calcifications. Olson and his associates⁹ studied similar lesions in an Ohio county and tried to prove that ascariasis was also a causative agent. They could not say that it was of any significance. Aleucemic leucemia, Hodgkin's disease, tuberculosis, sarcoid, lymphoblastoma, and brucellosis must also be

considered. H. L. Arnold, in Curtis' and Grekin's paper,¹⁰ cited that histoplasmosis showed some relationship to tuberculosis, sarcoid, Hodgkin's disease, and lymphoblastoma. He thinks that histoplasmosis, in blocking the reticulo-endothelium, causes an increase in susceptibility to other diseases. In lepromatous leprosy, which is essentially a reticuloendothelial disease, he states that in about 50 per cent of the cases the patients die of tuberculosis.

The treatment of histoplasmosis is rather discouraging. Various drugs, such as the sulfonamides and penicillin, have been of little value. Neostam, an antimony preparation, has been used by Mantell and his associates,¹¹ who obtained equivocal results. Since there was some improvement demonstrated, they believe it should be given further trial and study.

SUMMARY

Two cases of pulmonary calcification occurring in twins have been presented, the first patient having had symptoms since January, 1947, and the second being asymptomatic. In neither case has the etiological agent been identified. The tuberculin and coccidioidin skin tests in both children were negative, whereas the histoplasmin skin tests were positive. These cases may represent subclinical forms of histoplasmosis. When and in what locality the pulmonary calcifications first appeared is not known since the children have lived in many different states.

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Case Reports

CONGENITAL GOITER CAUSING DEATH OF A NEWBORN INFANT

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REMARKABLE enlargement of the thyroid gland in the newborn infant is unusual in the United States and practically a nonentity in the Great Lakes goiter belt. In Ohio and Minnesota, where there has been a high incidence of simple goiter, particularly before the period of iodine prophylaxis, the incidence of cretinism is low, and congenital goiter has not been reported up until 1939.¹

According to Solis-Cohen and Steinbach,¹ Means does not mention congenital goiter in his textbook on thyroid disease, and one finds no record of this condition in the reports of the Mayo or Crile clinics.¹ Only sporadic cases have been reported in the United States during the past twenty years. Recently Parmalee, Allen, Stein, and Buxbaum² reported three cases from the Chicago area, apparently the first from this vicinity.

Parmalee and his associates reported their cases because of the rarity of the condition and because in each instance the mother had taken iodine throughout her pregnancy. In their first case the child survived following oxygen therapy and iodine ointment locally, the gland becoming smaller on the sixth day of iodine treatment. In the second case the infant survived with no treatment for the first seventeen days, followed by desiccated thyroid gland, $\frac{1}{20}$ gr. once daily for several weeks. The third child had severe asphyxia, requiring tracheal catheterization at birth, and survived with no other treatment.

Dr. William H. Rubovits, who delivered the infant reported herein, recently described to me the following unusual case of congenital goiter. The infant was delivered a number of years ago in Chicago and unfortunately the complete record and photographs were lost. "A multigravida presented many of the objective findings of a twin pregnancy when examined abdominally in the third trimester. The uterine contents disclosed two bodies of equal size. An x-ray examination disclosed a single fetus with the occiput in the most extreme extension possible. With this information a re-examination confirmed the roentgenologic findings, that the fetus had a large tumor in the region of the thyroid. The patient went into labor at full term and cervical dilatation progressed rapidly. Intrauterine removal of an enormous cystic thyroid tumor was accomplished by morcellation, and the dead fetus was extracted. The tumor was about the size of a cantaloupe. The roentgenograms were presented to a colleague, an authority on thyroid disease, who unfortunately destroyed them."

The following case is reported because the goiter is one of the largest, if not the largest, on record in this country, and because the condition is so extremely rare in the Great Lakes region.

CASE REPORT

A male infant was delivered at term by cesarean section on April 17, 1947. Because of the critical condition at birth the infant was not weighed.

On delivering the head it was noticed that the head was retracted and the neck was markedly enlarged. The tongue protruded, and the facies were suggestive of cretinism. A huge mass was present in the thyroid region extending

From the Sarah Morris Hospital for Children, Michael Reese Hospital, Chicago.

laterally on both sides. All three lobes of the thyroid were greatly enlarged, smooth, and firm. There was inspiratory and expiratory dyspnea, and cyanosis was marked. A tracheal catheter was passed shortly after birth, and the cyanosis was relieved. However, dyspnea was only partially alleviated, as apparently the catheter relieved the obstruction incompletely. Bronchial breathing and moist râles were heard over both lower lobes. The heart was apparently normal, but was displaced to the left. An x-ray film revealed almost complete tracheal compression by the mass, which gave the appearance of a constricting collar (Fig. 1).



Fig. 1.—A large mass is present in the neck, completely encircling and compressing the trachea. At the level of the clavicles the trachea is only a narrow slit. The tracheal catheter can be visualized in the region of the posterior pharynx.

As a life-saving measure, a tracheotomy was performed by Dr. Oscar Becker two and one-half hours after birth. Immediately, the infant's color appeared normal and respirations were less labored (Fig. 2). The infant was placed in an oxygen tent, penicillin was administered, mucus was aspirated repeatedly through the tracheotomy tube, and the infant appeared to be doing well during the first twenty-four hours. However, approximately thirty-six hours after birth, the infant refused his feedings, respirations became shallow, cyanosis developed, and in spite of stimulants, the infant expired two hours later.

An autopsy was performed by Dr. Otto Saphir approximately eight hours after death. The essential pathologic findings were confined to the thyroid gland and the respiratory tract.

Autopsy Findings.—The body is that of a newborn male infant 52 cm. in length and weighing 2,900 Gm. Attention is directed to the neck where there is a pronounced swelling in the midline anteriorly. Beneath the skin there is a firm tumor which is lobed and freely movable in a lateral direction but immovable along the axis of the spine. The eyes have a piglike appearance. The tongue is not unusually large. There is a recent open tracheotomy wound. Both lungs are dark purple in color with few scattered zones of a pink color. They

are generally noncrepitant. The trachea is compressed below the thyroid cartilage and almost completely surrounded by a large, lobulated, firm, dark red tumor mass (Fig. 3). This can readily be dissected free of the anterior and midcervical fasciae. The mass measures 7 by 6 by 3.5 cm. and weighs 62 Gm. Attached to its posterolateral surfaces are two light, red-brown masses, measuring 3 mm. in diameter, which appear to be parathyroids. Below the inferior margin of the thyroid mass at a distance of 1.5 cm. is a tracheotomy wound. The trachea is entirely free of secretion. On cut section the thyroid presents a red, glistening surface divided into lobules by grey-white bands. It is well encapsulated.



Fig. 2.

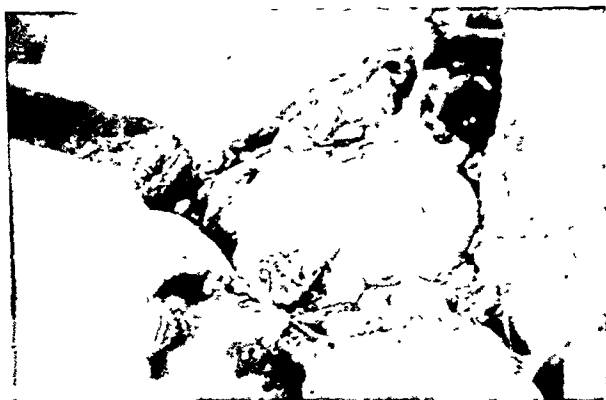


Fig. 3.

Fig. 2.—Tracheotomy two and a half hours after birth. The tongue appears slightly enlarged and protrudes. There is marked enlargement of the neck.

Fig. 3.—At necropsy the tremendous enlargement of all three lobes of the thyroid is well visualized.

Microscopic examination reveals that the alveoli and bronchi alike are filled with partially laked blood in all sections examined. There is little remaining air-containing lung. Scattered areas of collapse are also present. Blood pigment is deposited throughout the lung fields. The follicles of the thyroid gland are lined by cuboidal epithelium, making many infoldings. No colloid is present within their lumina. Little interstitial tissue supports the follicles.

DISCUSSION

According to Wegelin, the thyroid of normal infants in goiter belts weighs between 5 and 10 Gm., and rarely does an enlarged thyroid exceed 30 Gm.³ According to Saphir,⁴ in the Great Lakes region the thyroid gland of normal newborn infants weighs from 2.5 to 3 Gm. It is believed that the 62 Gm. thyroid in the case herein reported is the largest in the American literature. The thyroid of the infant reported on by Solis-Cohen and Steinbach¹ was 41 Gm.

In the case I have just presented, the gland almost completely encircled the trachea, causing marked compression, incompatible with life had not tracheotomy been resorted to. Unfortunately, hemorrhagic bronchopneumonia resulted in the death of the infant. It is believed that had not bronchopneumonia developed, the infant would have survived, probably with iodine therapy locally and/or internally and possibly subtotal resection as recently reported successfully by Davies⁵ on a 13-day-old infant who failed to respond to sodium iodine internally.

Histologically the thyroid presented the most common type of congenital goiter, namely, that of struma hyperplastica. There was an increase in gland lobules and also a filling of the follicles with a loose accumulation of cells. The thyroid did not present the appearance of a neoplasm.

There apparently is no adequate explanation for the etiology of sporadic congenital goiter. If iodine deficiency of the mother is the explanation, then it must be a question of faulty absorption or assimilation because the mothers of the infants reported on by Parmalee and his associates² had adequate iodine administration during pregnancy. Skinner prevented congenital goiter by feeding mothers iodine in an endemic area.⁶

SUMMARY

A case of sporadic congenital goiter weighing 62 Gm. is reported in a newborn infant. It is believed that this goiter is the largest of its kind reported on the American continent. A tracheotomy was successfully performed, but the infant died thirty-eight hours after birth from hemorrhagic bronchopneumonia.

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MACROCHEILIA FROM LABIAL GLAND HYPERPLASIA TREATED BY PLASTIC SURGERY

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THE commonest basis for chronic enlargement of the lips has long been considered as lymphangioma of congenital origin.¹ In our own practice we have more frequently encountered enlargement due to lymph stasis following burns, traumatic cicatrization, and even angioneurotic edema, persistent types of which have been recognized.² A less frequent cause seen by dermatologists is cheilitis glandularis, synonymously known as myxadenitis labialis. Most recently emphasis has been placed on an infrequent group of cases probably confused with cheilitis but in which the macrocheilia is now increasingly being accepted as a separate entity caused by hyperplasia of the labial salivary glands.^{3, 4} This report concerns such a case.

CASE REPORT

History.—J. H., a white boy 15 years old, was referred to us by his parents because of unsightly enlargement of the lower lip and left half of upper lip, which they correctly anticipated would aggravate his adolescence. The condition had been noted for three years and was slowly progressive. Itching, burning, or other subjective sensations were absent. There was no history of infections of the throat or mouth or of familial occurrence. Other aspects of the detailed history were irrelevant.

Physical Examination.—He was a well-developed, alert boy with marked swelling and tension of the lips causing considerable pouting, especially of the lower lip. This gave him a heavy, dull appearance so often associated with adenoids. On closer examination the mucosa of the lips for a distance of several centimeters from the vermilion border was studded with many pinhead-sized, ill-defined, somewhat elevated, hemispherical nodules, which felt firm to palpation and were somewhat paler than the adjacent tissue. No openings on the free surface were evident. There was no exudate on the mucosa. Tenderness and pain were absent. The buccal, lingual, and pharyngeal mucosa was normal. Serologic and hematologic studies revealed no abnormality.

A diagnosis of hyperplasia of the glandular structures of the lip was made and plastic surgery suggested therapeutically.

Operation.—

Upper Lip (Left Half): Local anesthesia. Infraorbital blocks. No novocaine injected in substance of left upper lip where hypertrophy was present. Incision made along lower border of mucous membrane extending from angle of mouth to midline. Labial artery palpated, retracted, but not incised. Excess mucous membrane predetermined and excised, removing a V-shaped mass of mucous glands and connective tissue. Mucous glands that presented in the field excised. Small bleeders ligated. Mucous membrane closed with fine silk sutures. Pressure bandage applied. Recovery uneventful.

Lower Lip Correction: The correction of the lower lip hypertrophy was done a few weeks later. Local anesthesia (bilateral mandibular blocks). Incision made on inner surface lingual to crest of lower lip. This incision extended from angle to angle of mouth. A similar incision made labial to previous incision, the width determined by hypertrophy present. Labial artery intact.

V-shaped mass of mucous membrane, mucous glands, and connective tissue removed. Many mucous glands presented on cut surface. These excised. Small bleeders ligated with catgut. Mucous membrane closed (silk), drawing labial surface inward to give normal contour to lower lip. Pressure bandage. Recovery uneventful.

Microscopic Examination.—The mucosal epithelium was somewhat thickened. There was moderate congestion and edema of the submucosa. Large nodules consisted of hyperplastic salivary glands of mixed type, which were sharply circumscribed. Small foci of lymphocytes and occasional plasma cells were seen in the stroma at the center of some of the glands. Large ducts were not distended.



Fig. 1.—J. H. five weeks after correction of left half of upper lip. Lower lip shows hypertrophy before surgery, more prominent on left side.

Hyperplasia of the labial salivary glands was the microscopic diagnosis.

Course.—Recovery was uneventful. When last seen in May, 1947, three years after the operation, the patient was 18 years of age and had weathered the critical adolescent period without self-consciousness or personality difficulties. He was successful in scholastic and athletic activities and well adjusted to home and school environment.

COMMENT

Interest centers about the fundamental nature of macrocheilia and its treatment.

No doubt in the older literature⁵ most cases were grouped with cheilitis glandularis apostematosa. In true cheilitis there is active mucosal inflammation in which even the cheeks and gums may be involved.⁶ Exudate may glue the lips together, and dilated ductal orifices have been described. While Volkmann believed the basic condition to be catarrhal inflammation of the labial glands, Sutton⁷ found the most prominent changes in the ducts.

Careful study of our case reveals neither clinical nor histologic evidence of inflammatory nature. Collections of lymphocytes do not necessarily indicate chronic inflammation when found at the sites shown in our case. Histologists⁸ accept lymphocytes and plasma cells in small numbers as normal constituents of the stroma of salivary glands.

Various investigators⁹ have considered glandular cheilitis as a precancerous disease in the sense of predisposing to malignant neoplasia. Sutton considered the basic condition adenomatous. Our case gave no impression of neoplasm, either benign or malignant, but rather strongly suggested a hyperplastic process.

Treatment by various authorities has run the gamut from iodide of potash internally, to local applications, roentgen rays, excision of individual nodules

with a punch, and finally plastic surgery. A critical survey of these methods has convinced us that plastic surgery is the most rational, safest, and most successful approach. The gratifying result in our case adds confirmatory evidence to the work of others attacking this same problem.

SUMMARY

A case of macrocheilia resulting from hyperplasia of the labial glands is reported. Cosmetic and psychologic difficulties led the patient to seek therapy. The shift in the concept of the underlying disease is discussed. The histologic picture is presented. The results of correction by plastic surgery were completely satisfactory.

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POLYCYSTIC DISEASE OF THE KIDNEYS IN A NEWBORN INFANT

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POLYCYSTIC disease of the kidneys is a condition very rare in childhood.¹ It is seen more often in stillborn or newborn infants. If born alive, the infant usually does not survive long, as there is not enough parenchyma to furnish adequate kidney function.

Sears² in 1926 reviewed the literature on the occurrence of polycystic disease of the kidney in the fetus and infant and collected eleven cases. In four cases the liver was also cystic; in the remaining seven this organ was not studied. In seven cases there were other deformities. Sears stressed the hereditary nature of the condition. Gruber³ believes that in the polycystic kidney of the fetus or the newborn infant there is usually an absence of a complete kidney pelvis. Cairns⁴ and others stress the familial and hereditary nature of the disease and list the defects with which it is most often associated, as harelip, spina bifida, atresia ani, and defects of the kidneys, ureters, and sex organs.

Our case is of more than usual interest in that there were no other congenital anomalies, the liver was normal, and the kidneys were unusually large.

CASE REPORT

B. S., a newborn white female, was seen about three hours following her birth. The mother's pregnancy and labor had not been remarkable until after the head was delivered. Then the obstetrician had considerable difficulty in delivering the abdomen because of its large size. He noted the presence of one or more large, firm, smooth masses in the infant's abdomen.

When seen by us the infant was a well-developed newborn child with an unusually large abdomen in which two large, firm, smooth masses could be felt. These extended from just below the costal margins to the level of the iliac crests on each side. They were of approximately the same size and appeared to meet but not to fuse in the midline anteriorly. They extended around posteriorly as far as the spine on each side. Examination was brief as the child became cyanotic and had to be returned to an oxygen tent. About two hours later the child expired (about five hours after delivery). At autopsy the abdomen was filled with two masses of about the same size occupying the positions of the kidneys. They were firm and smooth. When removed they were found to be kidneys, each measuring 9 by 5 by 6 cm. The right weighed 275 Gm., the left 285 Gm. (normal, 10 to 15 Gm.). There were no anomalies of the pelves or ureters. The urinary bladder was normal. The kidney capsule stripped with ease from a spongy, grey-red surface. On the surface made by cutting, the normal architecture was replaced by a spongy, grey-red tissue. There were individual, small, cystic spaces measuring from one to three millimeters in diameter and involving both the cortex and medulla. (Figs. 1 and 2.)

Microscopic sections of the kidneys showed cysts, lined by a single layer of flat, cuboidal epithelium. The wall of the cyst was loose connective tissue and there was some infiltration of neutrophils and eosinophils in the stroma. There were occasional small glomeruli, and some of the capillaries were filled with erythrocytes. There were only a few remaining tubules lined by columnar epithelium. In sections of the liver some of the sinusoids were filled with erythrocytes and immature red cells. No other unusual changes were noted. Microscopic sections of the other organs and tissues showed no notable deviations from the normal findings in newborn infants.



Fig 1.—Gross appearance of kidneys showing size and fetal lobulations.

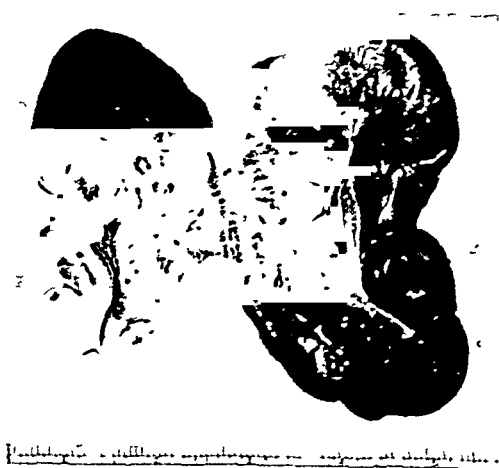


Fig. 2 —Cut section of left kidney.

SUMMARY

We have presented a case of bilateral polycystic kidneys of unusually large size, in a newborn infant who lived for only a few hours. There were no accompanying congenital anomalies, no cystic changes in the liver, and the kidney pelves were complete.

We are indebted to Dr. J. D. Bush for the pathologic reports.

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Medical Care

TREATMENT OF THE ANEMIAS OF INFANCY AND CHILDHOOD

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IN COMMON with all age periods, the contemporary treatment of the anemias of infancy and childhood has been marked by a greater selectivity of well-established drugs rather than by the addition of new antianemia agents. Except for folic acid, the effective remedies are still to be chosen from a list which includes iron, liver, transfusion, and splenectomy.

The trend toward more precise therapy stemmed from the introduction of liver in the treatment of pernicious anemia. This discovery inspired the hope that other anemias might reflect deficiencies of hematic factors similarly amenable to specific remedies. Although other agents of corresponding importance have not yet been isolated, expanding knowledge and the application of specialized techniques have made it possible to designate diagnostic criteria for specific hematologic entities heretofore loosely classified and inadequately treated. These investigations, embracing the whole life span, have served to focus attention on the peculiarities of the developing hematopoietic system in infants and children and on the need for considering these changes in evaluating hematologic aberrations in the growing period.

Antianemia therapy requires correction of the underlying cause, restoration of normal blood levels, and prevention of recurrences. The terms primary and secondary anemia are no longer tenable, since the symptom of anemia is always secondary to some known or unknown cause. In infants, the search for the basis of an anemia frequently extends into fetal life for an appraisal of such factors as the adequacy of iron storage, isoimmunization of the mother by fetal blood elements, the persistence of hemolytic processes following delivery, and the presence of maternal anemia. Recent studies which relate structural defects at birth to disturbances in the fetus may have their counterpart in the anemias of older children and adults, which may originate from defective antenatal development of the blood-forming organs. For example, the pathogenesis of sporadic cases of idiopathic hypoplastic and aplastic anemias and of hemorrhagic disorders in which the megakaryocytes are diminished or the capillaries inherently defective, may be due to fetal anomalies originating during critical periods of hematopoietic formation.

Following birth, hematopoiesis may be so affected and the blood picture so obscured by rapid structural and physiologic modifications of the hematopoietic system and other organs which are incident to the growth process itself as to

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complicate the interpretation of blood reactions in young persons, but the fundamental mechanisms involved in the pathogenesis of anemia are nevertheless common to all periods of life. Regardless of age, adequate treatment entails correction of deficiencies, elimination of underlying agents which depress the bone marrow, replacement of abnormal loss of red cells through hemorrhage or hemolysis, or removal of an organ which exercises an antagonistic influence on normal hematic processes.

A knowledge of the normal hematic values in the growing period is a prerequisite for gauging the need for antianemia treatment. Table I summarizes those values, which provide a working basis for comparative purposes, but it should be noted that for each age level normal infants and children exhibit a marked range of individual variation.

In all anemias measurement of the volume of packed red blood cells by the hematocrit constitutes an important and essential guide for diagnosis and therapy. This determination reflects the total mass of cells in a unit volume of blood and is the best single index of their size, shape, and thickness. The end point of antianemia therapy with specific agents or with multiple transfusions should strive for a volume of 36 per cent of packed red cells in the infant and younger child and 40 per cent in older individuals.

Therapy is inseparable from etiology, diagnosis, and classification. The judicious application of available antianemia agents implies an integrated concept of pathogenesis. During the period, however, when the nature of an anemia is under investigation, treatment need not be postponed. In the interim, orientation is aided by employing data from indirect sources. The relationships between the red cell count, hemoglobin, and the volume of packed red cells offer important clinical clues to treatment. The color index, a widely used measurement, represents the ratio of the hemoglobin level designated as the percentage of normal to the red cell count similarly expressed as percentage of normal. It defines the weight of hemoglobin in a single cell as compared with the content of a normal cell. A color index of approximately one is either normal or denotes an anemia for which transfusions are useful; an index of below 0.8 characterizes a hypochromic anemia for which iron is indicated; and an index of above one denotes macrocytic cells and an anemia which may be corrected by liver or folic acid or both. While the color index is in general a valid

TABLE I. NORMAL BLOOD VALUES IN INFANCY AND CHILDHOOD

<i>Hemoglobin</i>	
First day	20 Gm. (18 to 22 Gm.)
2 weeks	17 Gm.
First 2 years	11 Gm. (10 to 12.5 Gm.)
3 to 5 years	12.5 to 13 Gm.
5 to 10 years	13 to 13.5 Gm.
10 years to puberty	13.5 to 14.5 Gm.
<i>Red Blood Cells</i>	
First day	5,500,000 (5 to 6 million)
Second week	5,000,000
Older infant and child	4,000,000 per cu. mm. (lower limit of normal)
<i>Volume of Packed Red Cells</i>	
Infants and children	36% (lower limit of normal)
Older age groups	40% (minimum)

expression of the relationships between hemoglobin saturation and cell size, exceptions occur. In children, especially, the color index may be unreliable because of the normal fluctuations in hemoglobin and red cell counts which accompany growth.

More precise and instructive information regarding cell size and hemoglobin concentration in the younger age groups is obtained by measurement of the mean corpuscular volume and the mean corpuscular hemoglobin concentration. Their determination, usefulness in classification, and indicated therapy are described in Tables II and III.

TABLE II. MEASUREMENT OF RED CELL SIZE AND HEMOGLOBIN CONTENT

Mean R.B.C. volume, cubic microns* (normal M.C.V. = 80-94 cubic microns)	=	Volume of packed red cells (Hematocrit), c.c. per 1,000 c.c.
Mean hemoglobin concentration in R.B.C.† (normal M.C.H.C. = 32-38 per cent)	=	Red cell count, millions per cu. mm. Hemoglobin, Gm. per 100 c.c. \times 100 Volume of packed red cells, c.c. per 100 c.c.

*M. C. V.: More than 94 cubic microns—macrocytes; 80-94 cubic microns—normocytes; less than 80 cubic microns—microcytes.

†M. C. H. C.: Less than 32 per cent is hypochromic.

TABLE III. MORPHOLOGIC CLASSIFICATION OF ANEMIA* (FOR THERAPEUTIC ORIENTATION)

SIZE OF CELL	HEMOGLOBIN CONTENT	ANTI-ANEMIA AGENT
Normocytic	(a) Normal (Normochromic)	Transfusion
	(b) Reduced (Hypochromic)	Iron
Macrocytic	(a) Normal (Normochromic)	Liver and folic acid
	(b) Reduced (Hypochromic)	Liver, folic acid, and iron
Microcytic	(a) Normal (Normochromic)	Transfusion
	(b) Reduced (Hypochromic)	Iron

*Adapted from Wintrobe.¹

It will be observed in Tables II and III that the absolute values of hemoglobin concentration and mean cell volume provide practical guides for diagnosis and therapy. In the larger group of the anemias encountered in infancy and childhood, the hemoglobin concentration falls below the minimal normal value of 32 per cent (hypochromia), and for these patients improvement with iron therapy can be anticipated. Iron deficiency is usually accompanied by red cells of diminished size (below 80 cubic microns), and the blood smear reveals a predominance of hypochromic microcytes with pronounced central pallor. For the less common macrocytic anemias with mean red cell volumes ranging above 94 cubic microns, restoration to normal values can be expected with liver and folic acid therapy. It will be noted in Table III that macrocytes may either be fully saturated with hemoglobin or the pigment may be diminished, in which latter case iron therapy is also indicated.

In chronic infections and in systemic diseases such as nephritis, the red cells may be microcytic or normocytic with little or no decrease in the content of hemoglobin. These infections and diseases fail to respond permanently to antianemia therapy unless the primary cause is removed. Transfusions are symptomatically required for these conditions as well as for the normochromic and normocytic anemias resulting from bone marrow depression, such as

aplastic and hypoplastic anemias, and for leucemia in which marrow cell displacement occurs.

It may be profitable to review briefly certain principles of treatment with iron, folic acid, and transfusions. In addition, the anemias in which these agents serve a major therapeutic role will be considered in greater detail.

IRON

Iron Deficiency Anemia.—This anemia usually results from inadequate intake of dietary iron, infection, or blood loss, and the sole medicament usually required to correct this form of anemia is iron. The iron requirement has been stated to vary from 0.4 to 1 mg. per kilogram of body weight in early life to 0.2 to 0.4 mg. per kilogram for the older child, and the recommended intake to cover these requirements is 6 mg. for infants to 16 mg. per day for the adolescent.² It is obvious from Table IV that the suggested therapeutic dosage in terms of actual metallic iron content is greatly in excess of the requirements. Employment of the larger dosage covers the factors of irregularities in iron absorption. These include diminished gastric acidity, gastrointestinal disturbances, and changes within the intestinal tract resulting in the formation of insoluble ferric compounds less available for absorption. In general, ferrous iron salts produce higher increments of hemoglobin elevation than ferric salts in equal dosage. Two iron salts representative of those in common use in pediatric practice are recorded in Table IV.

The choice of iron preparations for the infant and young child depends on potency, ease of administration, inexpensiveness, and solubility. There are a large variety of iron salts—ferrous and ferric alike—that meet these requirements, and it is occasionally necessary to interchange them because of gastrointestinal irritation or anorexia produced by one or another preparation. With

TABLE IV. THERAPY OF THE ANEMIAS

ANTIANEMIA FACTORS		DAILY DOSAGE
<i>Iron</i>		
Ferrous sulfate	Infants, 4 to 6 gr. (0.25 to 0.4 Gm.)	
	(Syrup N.F.: 6 to 10 c.c.)	
Iron and ammonium citrate†	Children, 6 to 12 gr. (0.4 to 0.75 Gm.)	
	(Tablets U.S.P.:† 3 gr. each—0.2 Gm.)	
Iron and ammonium citrate†	1 to 1½ gr. per lb. (0.06 to 0.1 Gm.)	
	not to exceed a total of 30 gr. (2.0 Gm.)	
	(Capsules U.S.P.: 3¾ gr. or 7½ gr. each—0.25 to 0.5 Gm.)	
	10% in aqueous solution—1 c.c. per lb.	
<i>Copper (when indicated)</i>		
	0.25 to 1 mg. of copper sulfate per dose of iron	
<i>Liver Extract§</i>		
Oral: Powdered	12.75 Gm. = 1 U.S.P. unit	
	Liquid (U.S.P.)	45 c.c. = 1 U.S.P. unit
Intramuscular	1 to 15 U.S.P. units	
<i>Folic Acid§</i>		
Oral or intramuscular	5 to 20 mg.	

*Hydrous—20 per cent

†Excitoid—77 per cent

‡16.5 per cent

§Dosage of liver and folic acid on an individual basis.

} Metallic iron content

adjustments in dosage and care in technical details of administration a satisfactory hemoglobin level will be obtained with both ferrous and ferric salts alike. In the last analysis, the dosage of iron and other forms of antianemia therapy summarized in Table IV cannot be designated arbitrarily. The response to therapy as measured by the hemoglobin, red cell, and hematocrit levels determines the amounts to be administered.

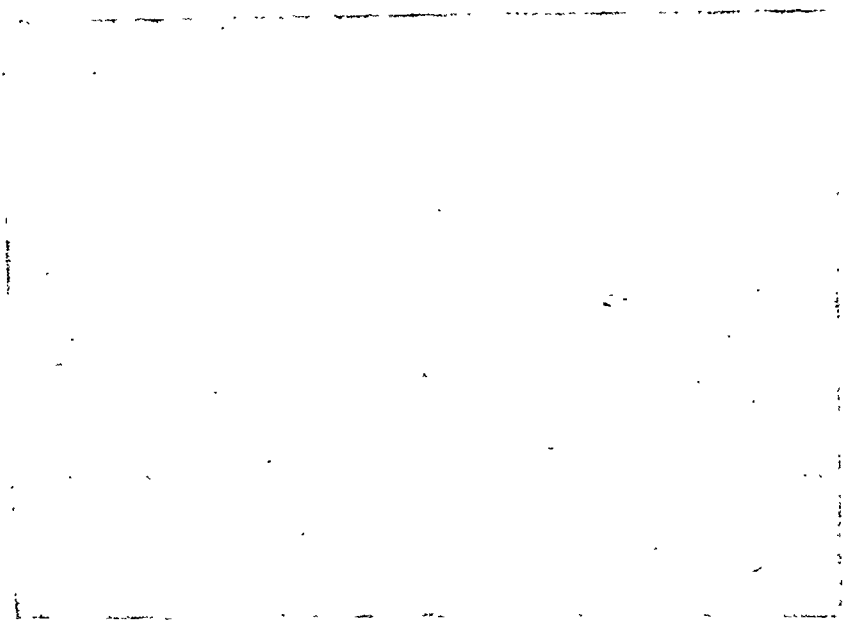


Fig. 1.—Photomicrograph of a blood smear of an infant of 18 months with iron deficiency anemia. Note predominance of hypochromic microcytes fairly uniform in size and shape, whose outstanding feature is the marked deficiency in hemoglobin content indicated by central pallor. Poikilocytes are also in evidence, and occasionally these take the form of oval cells. ($\times 1350$.)

Since a low hemoglobin constitutes the outstanding feature of the anemias of early life, the observed response to a therapeutic trial of iron serves to eliminate the condition based on a primary deficiency of this substance, which is usually initially considered. The blood smear in iron deficiency anemia (Fig. 1), characterized before treatment by the predominance of hypochromic microcytes which are fairly uniform in size and shape and markedly deficient in pigment, represents an additional guide for differentiation from other anemias (Table VI).

Copper.—In my experience it has not been necessary to employ copper in the treatment of nutritional anemia, although there are studies to show that its addition in minute traces results in prompt acceleration of hemoglobin production from a previously stationary level. In the occasional infant in whom copper deficiency may occur, as evidenced by a refractory state of the anemia, minute amounts of this element may be included in the iron prescription in the dosages noted in Table IV.

Gastric Acidity.—One of the factors which may call for maximum dosage of iron fortified by copper to secure normal hemoglobin levels is a diminished or absent free hydrochloric acid in the stomach. Normal gastric acidity is necessary for optimal absorption of iron from foods and iron preparations in all age periods, and hypoacidity may be a conditioning factor leading to iron deficiency anemia in infants and in children. Occasionally this abnormality persists even when the anemia is cured. Such children should be watched more closely for recurrence of anemia. There is a gap in our knowledge as to the onset of achlorhydria in adults who develop idiopathic hypochromic anemia and pernicious anemia, and those infants and children who secrete no acid following histamine may constitute some of the group with these anemias in later life. Administration of hydrochloric acid to these children is, however, without value in facilitating a cure of the anemia or in producing a response of the marrow as indicated by reticulocytosis.

The value of supplementation of iron with vitamins, folic acid, liver, or amino acids in uncomplicated microcytic hypochromic anemias in human subjects, contrary to animal experiments, is as yet unproved. When a hemoglobin response does not occur with adequate iron dosage and the morphologic appearance of the red cells is not restored to normal within three to four weeks, the probability is that the anemia is not based primarily on a deficiency of iron and should be reclassified. Iron deficiency can, of course, coexist with other anemias. This has been noted in patients with the trait and mild form of Mediterranean anemia.³ With adequate iron therapy an appreciable elevation of hemoglobin occurs in these patients, but the basic blood picture of Mediterranean anemia remains.

Vitamin C.—Since iron is absorbed in the ferrous form, the reduction of ferric salts to the bivalent form depends upon reducing mechanisms present in the small intestine. Moore and his associates⁴ demonstrated that the ingestion of vitamin C together with ferric salts resulted in an increase in serum iron, probably by its reducing action. On the other hand, in a recent study of children of school age, Schulze and Morgan⁵ employed soluble ferric pyrophosphate and small supplements of copper and found that the addition of ascorbic acid was unnecessary for the synthesis of hemoglobin.

Infection.—Infection and dietary deficiency⁶ comprise the two most frequent etiological factors in the anemias of infancy and childhood. The anemia of chronic infection previously ascribed to toxic inhibition of hematopoiesis, defective iron absorption, or blood destruction has been found by Wintrobe and his associates to be associated with reduced plasma iron content, an elevation of serum copper, and a rise in erythrocyte protoporphyrin. They showed that the presence of infection led to a rapid withdrawal of iron from the plasma and an augmented diversion to the ordinary storage tissues, mainly the liver.⁷ The microscopic appearance of the red cells in infection is summarized in Table VII.

Inadequate Intake of Iron-containing Foods.—Since both human and cow's milk contain relatively small amounts of iron, prolonged lactation and a predominantly milk diet represent outstanding causes of iron deficiency anemia.

Correction of the anemia in these instances consists of the administration of medicinal iron in adequate dosage, a reduction in milk intake, and the introduction of foods capable of replenishing hemoglobin.

Anemia of Prematurity.—In the premature infant, the postnatal drop of hemoglobin and red blood cells from the polycythemic levels at birth is usually greater and more prolonged than in the full-term infant. The fall in hemoglobin content exceeds that in red cell count. No intrinsic defect in hematopoiesis in the premature infant corresponding to the specific aberrations in the metabolism of aromatic amino acids described by Levine and his associates⁸ has been discovered. Except for relatively smaller iron stores, the lowered blood levels reflect an exaggeration of the same physiologic processes that operate in the infant born at term. The more rapid rate of body growth in the premature infant leads to expansion of blood volume and dilution of circulating hemoglobin. Excessively lowered blood levels, however, do not occur uniformly in all premature infants. When present, it may be assumed that the rate of hematopoiesis and the amount of reserve iron are inadequate to meet their greater needs. Iron alone or in combination with other hematinics has been prophylactically administered soon after birth and elevated blood levels have been reported, but unequivocal rises were not noted until the second to the third month.⁹ Findlay¹⁰ has recently discouraged the routine use of iron early in life—first, because not all premature infants regularly develop severe grades of anemia, and second, because there is a natural tendency for a rise in blood levels. He administered iron in a dosage of from 20 to 60 mg. daily in the form of ferrous sulfate within the first ten days of life and noted a slight but definite rise in hemoglobin from the fifth to the eighth months (Fig. 2). At one year of age, however, there was no statistical difference between the blood pictures of the treated and untreated infants, although earlier and more sustained rises have been observed by other investigators.⁹ Since the response to iron therapy in the early neonatal period is equivocal, it would seem preferable to limit the administration of iron to those premature infants who show subnormal hemoglobin levels at 2 to 3 months of age when the bone marrow is more responsive to stimulation. In an occasional infant in whom postfetal hemolysis is concluded before 2 months and subnormal blood levels are established, iron therapy may be instituted at an earlier age. In the event of gastrointestinal disturbances, transfusions of blood are preferable.

FOLIC ACID (PTEROYLGLUTAMIC ACID)

Folic acid, the recently isolated and successfully synthesized *Lactobacillus casei* factor, has been shown by extensive trial to possess a striking antianemia effect in pernicious anemia and in a variety of macrocytic anemias of nutritional origin. Macrocytic anemias responsive to liver therapy are rarely encountered in infancy and childhood, so that this new therapeutic agent still occupies a restricted field of usefulness in pediatric practice.

Authentic cases of pernicious anemia resembling the adult disease are rare in children. Less infrequent are the macrocytic anemias observed in some in-

fants with acute infection,¹¹⁻¹³ in congenital malformations of the intestine, and in such chronic diseases of the gastrointestinal tract as celiac disease, in which absorption of antianemia principles is impaired. In these juvenile patients the anemias have heretofore been successfully treated with injections of liver extract.

HEMOGLOBIN PERCENTAGE CONCENTRATION IN PREMATURE INFANTS WITH AND WITHOUT ADDITIONAL IRON (FINDLAY)

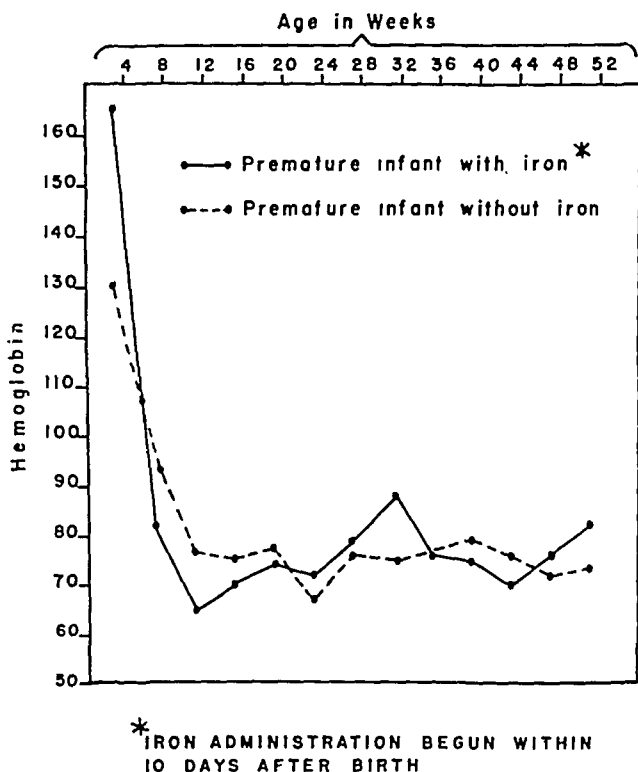


Fig. 2.—Hemoglobin percentage concentration in premature infants with and without additional iron (modified from Findlay.¹⁰)

Except for the group of megaloblastic anemias described by Zuelzer and Ogden,^{14, 15} folic acid has not been intensively investigated in the anemias of infancy and childhood. Peterson and Dunn^{16, 17} demonstrated the effectiveness of folic acid in a child whose clinical course and laboratory data satisfied the criteria for a diagnosis of pernicious anemia. This patient, whose anemia had been controlled with injections of liver extract, showed a comparable hematologic response when given 10 mg. of synthetic folic acid per os daily. There is evidence that a daily dosage of 5 to 20 mg. of synthetic folic acid by mouth or by injection as prescribed for adults may be extended to infants and children.

An advantage of folic acid over liver extract is that oral administration is as satisfactory as parenteral injection.

Megaloblastic Anemia of Infancy.—This entity was described by Zuelzer and Ogden^{14, 15} in infants from 2 to 16 months old in whom respiratory symptoms and gastrointestinal disturbances were common complaints. The condition is characterized by a normochromic and usually macrocytic anemia, leucopenia, neutropenia, and thrombocytopenia. The bone marrow reveals a megaloblastic type of erythropoiesis and changes in the granulocytes resembling those of pernicious anemia. Of twenty-nine patients with this syndrome,^{14, 15} twelve were treated with folic acid in a dosage of 5 to 20 mg. daily, over a period of from eight days to three weeks. The effects of folic acid were indistinguishable from the effects in patients treated with liver extract. From the third to the fourth days the reticulocytes began to rise; shortly thereafter the hemoglobin and red cell count improved, neutrophils and platelets increased in number, and the bone marrow assumed a normal pattern within a few days after institution of therapy. In one instance the bone marrow showed a complete reversal of the megaloblastic appearance two days after the first injection of folic acid. In contrast to pernicious anemia, the deficiency is not a permanent one and is completely cured without relapse.

Aplastic and Hypoplastic Anemia.—Accumulating evidence emphasizes the specificity of synthetic folic acid in promptly transforming a megaloblastic bone marrow into the normal normoblastic pattern. In anemias with normoblastic, hypoplastic, and aplastic bone marrows the results have been disappointing. The multiple effects of folic acid, observed in animals rendered pancytopenic by deficiency diets, in restoring granulocytes, platelets, and red cells to normal levels have not been demonstrated in human subjects with hypocellular bone marrows. Nevertheless, Doan's investigations¹⁸ indicating that folic acid probably supplies a fundamental molecule essential to the normal metabolism of all cell types in the bone marrow may explain the occasional reports of the value of this hematopoietic principle in anemias accompanied by hypoplasia of the bone marrow.

In three adult patients studied by Gendel¹⁹ with a peripheral blood picture of pancytopenia, the hemoglobin and red cell values were significantly elevated when the daily oral dose of synthetic folic acid was increased to approximately 200 to 400 mg. Peat²⁰ noted that the interval between transfusions in a patient 18 years old with hypoplastic anemia, who was observed for nine years, was lengthened when transfusions were supplemented with the folic acid fraction of liver. On the other hand, resistance to treatment in this type of anemia is illustrated by an infant of one year now under observation whose bone marrow reveals depression of erythropoiesis exclusively and in whom a daily oral dose of approximately 15 mg. of synthetic folic acid (pteroylglutamic acid) has been ineffective in producing a reticulocytosis or in alleviating the anemia. Nevertheless, it is advisable to subject all patients with aplastic and hypoplastic anemias to a therapeutic test of folic acid in large dosage. Such therapy should, however, be administered with caution because of the recently expressed

opinion concerning the possible deleterious influence on the nervous system.²¹ This group of anemias will be discussed further in the section on transfusions.

TRANSFUSIONS

Erythroblastosis Fetalis.—The practice of transfusing infants with erythroblastosis with Rh-negative blood at birth or soon thereafter is firmly established. Routine treatment consists of either repeated transfusions of Rh-negative blood or the subtotal replacement of the Rh-positive blood of the baby by Rh-negative blood.

The fractional method of treatment entails multiple transfusions of blood in amounts of approximately 20 c.c. per kilogram (10 c.c. per pound) of body weight. Experience has shown that after the fifth or sixth day maintenance of levels of 10 to 12 Gm. of hemoglobin per 100 c.c. of blood is preferable to the 16 to 20 Gm. that characterize the early newborn period. Despite the success of this form of treatment in reducing mortality, it has the objection that free circulating antibody continues to interact with remaining agglutinable red blood cells. This protracted hemolysis may demand a continuing supply of additional increments of Rh-negative blood as needed, and carries the potential hazard of irreversible damage to the liver, brain, and kidneys from the products of red cell disintegration. Less frequent pathologic changes include hemorrhagic disorders, biliary obstruction from excessive hemolysis, and conceivably mental retardation from nerve cell injury.

Exsanguination Transfusion.—Exsanguination transfusions represent a prophylactic measure designed to eliminate the need for repeated transfusions and the sequelae of hemolysis. In this procedure the major portion of the affected infant's blood containing free antibodies in the plasma and Rh-positive cells with and without a coating of antibody is replaced by normal plasma and Rh-negative cells. Such replacement has in a growing experience been effective in arresting the course of the disease in the postnatal period, but its failure to influence the development of kernicterus presupposes antecedent tissue damage not amenable to treatment. Preliminary studies indicate that the infants with extremely high peripheral nucleated red cell counts who usually succumbed with earlier methods are more likely to survive when treated with one of the exsanguination procedures.²²

Methods: The replacement of blood, which has until recently been regarded as a heroic measure, is now performed routinely in many clinics. The technical steps involved in each of the exsanguination-transfusion procedures in current use and the amount of blood to be replaced are still undergoing modification. The use of the longitudinal sinus originally proposed by Wallerstein²³ for the removal of blood may be replaced by the less hazardous technique of permitting free bleeding from an incision of the radial artery. In the method advocated by Wiener and his associates,²⁴ Rh-negative blood is infused into the saphenous vein, and blood is simultaneously withdrawn from the radial artery. The simplest procedure, devised by Diamond,²⁵ consists of alternately withdrawing and injecting blood through a special plastic catheter inserted in the umbilical

vein. If mechanical difficulties are encountered or if this vein is not available, the exchange of blood can be similarly carried out by using the saphenous vein at the thigh and directing the catheter into the larger venous channels.

Criteria for exsanguination transfusion: The risk of replacement transfusions immediately after birth emphasizes the importance of establishing proper criteria in the choice of patients. In recent years, attempts to prognosticate the type and severity of erythroblastosis at birth from the serologic findings in the mother during pregnancy and from the hematologic picture and to a lesser extent from the serologic features in the infant have thus far been confusing. Yet, proper assessment of these data provides the indications for a procedure in which few are relatively expert at present.

Comparison of the clinical and serologic criteria designated by several of the larger clinics for exchange transfusions reveal a lack of unanimity. The basic indications for this procedure suggested by Diamond²⁷ are in accord with current experience. Exsanguination transfusions are recommended by him for two groups of infants whose mothers are known or can be quickly demonstrated to have Rh antibodies in their serum: infants who at or shortly after birth have clinical signs of full-blown erythroblastosis and who have anemia, jaundice, splenomegaly, and hepatomegaly; and Rh-positive infants who are clinically normal at birth but who reveal free antibody in the cord blood. Despite the absence of anemia at birth in these latter infants, the course may rapidly change: jaundice and anemia become increasingly pronounced, often with a fatal outcome. Replacement transfusion is unnecessary in an Rh-positive infant who appears normal, is not anemic, and in whom no free agglutinins are found in the serum even though the mother shows Rh antibodies during pregnancy.

Detection of Sensitized Infant's Red Cells.—The demonstration of passively transferred maternal antibody in the cord blood and in the infant's serum at birth and of red cells coated with Rh antibodies is particularly important in deciding on the potential severity of the case of erythroblastosis and of the type of therapeutic procedure to be employed. The detection of in vivo sensitization of the infant's red blood cells by maternal Rh antibody is especially useful when the mother's blood has not been tested during pregnancy, or if these data are not immediately available, or when the results of the tests in the mother have been equivocal. Sensitization of the red cells of the infant has been recently investigated by techniques involving separation of absorbed antibody from the red cells by elution,²⁶⁻²⁹ by agglutination,³⁰ and by agglutination with the use of the sera of rabbits immunized against whole human serum or human globulin. In the last procedure, devised by Coombs and his associates,²¹⁻²³ the Rh-positive cells of the infant presumably coated with agglutinins or blocking or "incomplete" antibody are made to agglutinate strongly on the addition of the antihuman serum or globulin. This method, also designated as the "developing test," promises to become an essential guide both in determining the degree of involvement of the red cells and the need for replacing the blood of the affected infant. While this test may prove to be specific for erythroblastosis it should be pointed out that the same testing serum has been found to agglutinate the red cells in cases of acquired hemolytic anemia.²⁴⁻²⁶ Whether the

detection of red cells in the infant coated with anti-Rh antibody alone is a sufficient indication for replacement transfusion or whether free maternal antibody in the serum is also a prerequisite remains to be proved.

Termination of Pregnancy.—Under certain circumstances pregnancy may be terminated by the induction of labor with immediate exsanguination transfusion of the baby. This procedure has been recommended in a woman who has a homozygous husband and a history of repeated stillbirths or miscarriages in the latter half of pregnancy, the loss of one or more infants with erythroblastosis, and a high or a rising titer of maternal antibody. If the husband is heterozygous, under similar circumstances the pregnancy may be allowed to go to term, and the condition of the infant will determine the need for replacement with Rh-negative blood. The decision for the early termination of pregnancy by induction or cesarian section must be weighed carefully; since maternal antibodies already have been transmitted and the newborn infant then faces the double hazard of erythroblastosis and immaturity. The advisability of premature induction of labor is still debatable and awaits further study and accumulation of data.

It is obvious that the indications for exsanguination transfusion require individualization based on an appraisal of clinical, hereditary, and immunologic factors. It is anticipated that sufficient statistical data will soon be available to compare the results of treatment employing multiple transfusions of Rh-negative blood with the method of exsanguination and replacement, and that this analysis will furnish more precise criteria for each procedure.

Outpatient Transfusions for Ambulatory Patients With Chronic Anemias.—The establishment of an outpatient transfusion clinic at the New York Hospital^{37, 38} was prompted by the large numbers of children with the severe form of Mediterranean anemia who required frequent administrations of blood. Experience since 1944 has amply confirmed its many anticipated advantages. The elimination of repeated hospitalizations has permitted the normal continuity of home and school life. Transfusions at regular intervals assure the maintenance of continuously adequate blood levels and are sounder practice than the replenishment of a depleted blood supply at irregular intervals. Hospital administration has benefited by the reduction of costs and the more effective utilization of available bed space for acute needs.

Originally planned for the treatment of advanced cases of Mediterranean anemia, the clinic now includes patients with sickle cell anemia, hypoplastic and aplastic anemias, hemorrhagic disorders, and leucemia. The types of anemia treated in such a clinic will vary with their prevalence in the particular community.

Procedure: Before a child is accepted for outpatient treatment, preliminary admission to the inpatient service is desirable. During this stay daily transfusions are given until the hemoglobin is elevated to 13 Gm. and the hematocrit reading is 38 to 40 per cent. Two weeks following discharge, outpatient transfusions are begun and are subsequently given at fortnightly intervals.

TABLE V. PROCEDURE FOR OUTPATIENT TRANSFUSIONS

Inpatient (Preliminary Admission)

Daily Transfusions Until Optimum Values are Obtained:

Hemoglobin 13 Gm.

Hematocrit 38 to 40 per cent

Outpatient

Transfusions:

(a) Begin 2 weeks after inpatient discharge.

(b) Repeat fortnightly.

Amount of Blood Given Each Visit:

*Weight**Amount*

Under 12 kg. (about 26 lbs.)

20 c.c./kg. (10 c.c./lb.)

12 to 20 kg. (26 to 44 lbs.)

250 c.c.

Over 20 kg. (44 lbs.)

300 to 500 c.c.

Average Blood Levels Before Transfusion:

Hemoglobin 9 to 11 Gm.

Hematocrit 27 to 32 per cent

Although optimum hemoglobin and hematocrit levels are desirable for maximum cardiovascular efficiency, they are difficult to attain in chronic hemolytic, hypoplastic, or aplastic anemias. Experience in the transfusion clinic with patients in whom Mediterranean anemia has become arrested has shown that certain minimal blood levels are compatible with resistance to infection, performance of normal activities, and growth in younger persons. These blood levels are 9 to 11 Gm. of hemoglobin per 100 c.c. of blood and a hematocrit value ranging between 27 and 32 per cent. These values serve only as a general guide, and in individual patients more desirable levels may be attained by varying the amount of blood and the interval between transfusions. In severe nutritional anemia, for instance, it should be possible to maintain a hemoglobin of 13.0 Gm. and a hematocrit of 38 per cent with supplemented specific anti-anemia therapy.

The amount of blood injected varies with the age and weight of the child. A child weighing less than 12 kilograms (about 26 pounds) receives 20 c.c. of blood per kilogram of body weight (approximately 10 c.c. per pound). Between 12 and 20 kilograms (26 to 44 pounds) the total amount given is 250 of blood, and above 20 kilograms, 300 to 500 c.c. When blood levels before transfusion are well above the minimal threshold (Table V), treatment is postponed for an additional two weeks. Occasionally, transfusions are given at weekly intervals, especially in the absence of preliminary hospitalization. Originally Type O red cells resuspended in isotonic solution of sodium chloride were employed. At present, whole bank blood of compatible group and Rh type is used. The essential features of the out-patient transfusion procedure are summarized in Table V.

If reactions occur, they take place usually within an hour after completion of transfusion. They include abdominal pain, chills, fever, headache, and more rarely, urticaria, asthma, and occasionally evidences of hemolysis. No reactions have been severe enough to require hospitalization or discontinuance of ambulatory therapy.

Aplastic, Hypoplastic, and Chronic Congenital Aregenerative Anemias.—In considering the treatment of this group of diseases, it is advisable to review

the distinctive hematologic features. Aplastic anemia is a chronic progressive disease, characterized by simultaneous depression of the three principal cellular elements in the bone marrow, and resulting in a peripheral blood picture of profound anemia, leucopenia, neutropenia, and thrombocytopenia. Hypoplastic anemia differs from aplastic anemia in that the formation of red blood cells is impaired with lesser involvement of the granulocytes and platelets, and these distinguishing features are usually reflected in the bone marrow.³⁹ Chronic congenital aregenerative anemia, frequently classified with hypoplastic anemia, can be separated from it by the failure of erythropoiesis alone, while the formation of the granulocytic elements and platelets is entirely unimpaired. Although hypoplastic anemia implies a less severe course and occasionally a more hopeful outcome than aplastic anemia, the term has nevertheless been applied in recent years to intermediate conditions in which the three blood elements of the bone marrow are involved in variable degree. Estren and Dameshek⁴⁰ have recently described as hypoplastic anemia, familial cases with generalized quantitative hypoplasia of all the elements in the bone marrow with the nucleated red cells in normal or elevated percentages. In one of their patients with an increased number of reticulocytes and thrombopenia, splenectomy resulted in moderate clinical hematologic improvement.

Chronic congenital aregenerative anemia: The elucidation of the factors involved in the causation of chronic congenital aregenerative anemia will be facilitated by removing it from the general category of hypoplastic anemia and restricting the term to patients in whom the only abnormality consists of an absence of nucleated red cells in the bone marrow and in whom the other formed elements are qualitatively and quantitatively unaltered. This unusual feature, of a single cell type which is depressed without affecting the elements in close anatomic proximity, constitutes the cardinal characteristic of this hematologic entity, and is illustrated by the following case history: In an infant one year old, under observation at present, the peripheral blood and bone marrow have consistently presented the hematologic picture of aregenerative anemia. The anemia dated from birth and presented the clinical features of mild erythroblastosis. The blood group of the mother was Landsteiner, Group O, Rh positive, and of the infant, Group A, Rh positive. Appropriate tests showed that the infant was a nonsecretor. The anti-A titer of the mother's serum when the infant was 2½ months of age was reported as 1:128,000 and dropped three weeks later to between 1:640 and 1:1,280. Repeated blood transfusions have been the mainstay of treatment. It is conceivable that erythropoiesis in the fetus may have been impaired by the prolonged reaction with an antibody in high titer against its own red cells in the course of an incompatible pregnancy. The hypothesis that a depression in red blood cell production results from an antigen-antibody reaction occurring in fetal life requires further corroborative evidence. Levine⁴¹ has stressed the possibility of early isoimmunization with the A and B factors in incompatible pregnancies in the first months of fetal development. The circumstances noted in this patient may be unique, but they afford a basis for further investigation of the development of this unusual blood dyscrasia. This case will be reported in greater detail in a subsequent communication.

Except for the occasional cases in which improvement follows splenectomy, periodic transfusions constitute the sole reliable therapeutic measure for aplastic, hypoplastic, and chronic aregenerative anemias. Instances are on record in which after years of transfusion spontaneous recovery has occurred in hypoplastic and chronic congenital aregenerative anemias without further need for supportive treatment.^{42, 43}

In Tables VI and VII is summarized the specific treatment of the common anemias encountered in infants and children in whom the antianemia agents that have been discussed are employed. The essential diagnostic features of the respective blood smears have been included since their accurate interpretation contributes in large measure to effective treatment.

SUMMARY

The judicious administration of an antianemia agent implies not alone the restoration of normal blood levels but an inquiry into the pathogenesis of the anemia with a view to correcting the underlying cause. In this paper the treatment of anemias was integrated with a consideration of etiology and diagnosis.

TABLE VI. ANEMIAS OF EARLY INFANCY

TYPE OF ANEMIA	DIAGNOSTIC FEATURES OF THE BLOOD SMEAR	TREATMENT
Erythroblastosis fetalis	Hyperchromic macrocytes, nucleated red blood cells	Transfusions
Hemorrhagic anemia	Acute blood loss; normochromic and normocytic red blood cells	Transfusions
	Chronic blood loss; hypochromic microcytes	Iron
Iron deficiency anemia	Hypochromic microcytes, marked central pallor of red blood cells, poikilocytes	Iron
Anemia of prematurity	Early, normocytic and normochromic red blood cells; later, hypochromic microcytes	Iron
Megaloblastic anemias of infancy	Very large macrocytes, microcytes, occasional nucleated red blood cells, abnormal neutrophils	Liver, folic acid

TABLE VII. ANEMIAS OF LATER INFANCY AND CHILDHOOD

TYPE OF ANEMIA	DIAGNOSTIC FEATURES OF THE BLOOD SMEAR	TREATMENT
Anemia of infection	Normocytic and normochromic, occasionally microcytic and hypochromic red blood cells. With iron deficiency hypochromic microcytes predominate	Iron and transfusions
Aplastic, hypoplastic, and aregenerative anemias	Normochromic and normocytic red blood cells	Transfusions, splenectomy (?)
Congenital hemolytic anemia	Spherocytes and large number of reticulocytes	Splenectomy
Sickle cell anemia	Sickle cells, target and oval cells, hypochromic macrocytes	Transfusions, splenectomy (?)
Mediterranean anemia, severe type	Very large thin hypochromic macrocytes, nucleated red blood cells, marked poikilocytosis, and anisocytosis	Transfusions, splenectomy (?)
Mild type or trait	Hypochromic macrocytes, basophilic stippling, polycythemia, target and oval cells	None

In infants, for instance, the basis of an anemia requires a search of the fetal period for an appraisal of the adequacy of iron storage, for evidences of maternal isoimmunization by fetal blood elements, for anemia in the mother, and for possible extrinsic causes which may have interfered with the normal continuity of antenatal development of the blood-forming organs.

In contrast to adults, in whom blood levels are static, reference must be made to normal hematic values of corresponding periods of growth in determining the need for treatment and the efficacy of an antianemia agent in infants and children.

Pending recognition of the nature of the anemia, interim treatment may be given. Orientation can be facilitated by employing data from indirect sources. The relationships between the red cell count, hemoglobin, and the volume of packed red cells offer important clinical clues to treatment. The mean corpuscular volume and the mean corpuscular hemoglobin concentration are practical guides for diagnosis and therapy in various groups of anemias. Conversely, the color index may prove unreliable in infants and children because of the physiologic fluctuations in hemoglobin and red cell counts with age.

Recent advances in iron, folic acid, and transfusion therapy were reviewed in relation to the anemias of infancy and childhood. In common with all age periods, these advances have been marked by a greater selectivity of well-established drugs rather than by the addition of new antianemia agents.

The choice of treatment of erythroblastosis by replacement or repeated small transfusions was discussed. A review of the methods and major indications for exsanguination transfusion indicate that many aspects of this form of therapy are in the process of development and evaluation.

The organization of an outpatient transfusion clinic for the treatment of chronic anemias was described. The benefits to the anemic child and the practical advantages to hospital administration have been amply shown in the experiences at the New York Hospital.

In the therapy of the group of aplastic anemias, it was pointed out that chronic congenital aregenerative anemia should be separated as a hematologic entity distinct from hypoplastic anemia. The evidence in a case history that was cited suggested that the pathogenesis of chronic congenital aregenerative anemia, an unusual blood disorder, might be related to early isoimmunization with a blood-group factor in an incompatible pregnancy. The hypothesis that a depression in red cell production results from an antigen-antibody reaction occurring in fetal life is far-reaching and requires further investigation.

Finally, the specific treatment of the common anemias in infancy and childhood was summarized in conjunction with the diagnostic features of the respective blood smears.

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Clinical Conference

CLINICOPATHOLOGIC CONFERENCE AT THE HOSPITAL FOR SICK CHILDREN

TORONTO, ONT.

W. L. DONOHUE, M.D., DIRECTOR OF PATHOLOGY

Dysendocrinism

DR. D. R. CLARK (House Physician).—

History.—The patient, a full-term white female infant with a birth weight of only 3 pounds 14 ounces, was admitted at 27 days of age, her weight having decreased to 3 pounds. The mother, a primipara, aged 28 years, stated that during the seventh month of pregnancy her abdominal enlargement ceased and even retrogressed to such a degree that friends asked whether or not she had delivered her child. Intrauterine fetal movements practically ceased at this time. At term there was a medical followed by a surgical induction. The child had one cyanotic attack at birth. The baby made slow progress until seven days prior to admission to the Hospital for Sick Children, at which time the abdomen became distended. Respirations were shallow and rapid, and there was slight cyanosis. At this time some red lumps appeared over the body and extremities. The abdominal distention was not improved by enemas. Due to failure to gain, various feedings were tried with no improvement. The maternal grandmother was a diabetic. The mother states she was allergic to dust during her pregnancy only. The parents are second cousins.

Physical examination revealed an underdeveloped, poorly nourished female infant with a peculiar facial appearance. The eyes were widely spaced and prominent, the ears large, and the hair abundant, giving the face a peculiar elfin appearance (Figs. 1 and 2). The skin was loose, lying in folds, and there was obvious muscular wasting. Both the skin and hair were dry. Hydration was fair, but there was scanty subcutaneous fat. There were several red raised areas, which were soft and freely moveable and varying in size up to 2 cm. in diameter over the scalp, forehead, and back. The cranial sutures were separated. There were no signs of an upper respiratory infection or cardiovascular abnormalities. The umbilicus was covered with a dry crust, and the surrounding skin was slightly injected. The border of the liver was barely palpable. Both kidneys were palpated, and each appeared to be the size of a small lemon.

Laboratory Investigation.—Urine: trace of albumin with occasional red blood cells and white blood cells. On two occasions sugar was found in the urine, but this may have been due to intravenous therapy. Blood: red blood cells 5.4 million; white blood cells 16.3 thousand; hemoglobin 15.8 Gm. per cent; film normal. N.P.N. 29.0 mg. per cent. Creatinine 0.75 mg. per cent. Urine culture: bacilli of colon group. Blood culture negative.

From the Departments of Pathology and Paediatrics, the Hospital for Sick Children and University of Toronto.

X-ray Investigation.—Two excretory urograms were unsuccessful due to a considerable amount of gas in the stomach and small bowel. The lungs showed emphysema, bronchiolitis, and interstitial pneumonitis. The skull showed increased width of the sutures, which was interpreted as being due to retarded bony maturation.

Treatment and Progress.—The subcutaneous abscesses cleared satisfactorily on intramuscular penicillin therapy. The infant took feedings fairly well, had two to five soft yellow stools per day, and had a very slight weight gain. She was sent home on the sixteenth hospital day (7½ weeks of age) as she was free from infection. She was readmitted the following day because of coughing. During her short period at home she had two attacks of cyanosis. Condition on readmission was as before except that there was a rough, systolic cardiac murmur along the left border of the sternum. The infant's condition rapidly deteriorated for no obvious reason, and she died two days following her readmission.

The clinical diagnosis was dystrophy, progeria, multiple congenital malformations of head, face, heart, and kidneys, with possible gargoylism.

DR. H. E. EDWARDS (Staff Physician).—I first saw the child when she was 4 weeks of age. Apparently the infant was born after a medical followed by a surgical induction. Shortly after birth she had one blue spell. According to the information I received, abdominal distention had become marked on the seventh day of life, and this was not relieved by enemas. She had not gained or made satisfactory progress on several different formulas. I advised that the child be admitted here.

DR. W. L. DONOHUE (Director of Pathology).—The post-mortem findings in this case were most bizarre and do not fit into the pattern of any condition which we can recall having seen previously. The body was extremely emaciated and undersized, measuring only 45 cm. in length; the normal length of a full-term infant 7 weeks old is approximately 54 cm. As noted clinically, the child had a peculiar appearance. The hair on the head was dark brown, fine, and abundant. There was a definite hair line at the forehead, but fine downy brown hair was present over the forehead extending as low as the eyebrows. Anterior to the ears, the hair extended low on the cheeks. Excessive lanugo was present over most of the body. There was no pubic hair. As may be seen from the photographs of this child the facies was unusual; the external ears were much larger than normal; the eyes were large, prominent, and widely spaced; the nose was retuse, broad at the tip, with flaring nostrils; the mouth was large with thick prominent lips. The mammae were enlarged, and the nipples were prominent. In each breast there was a firm disclike mass measuring approximately 2.5 cm. in diameter and 1 cm. in thickness. The abdomen was distended. The emaciation had resulted in abnormal prominence of the labia minora, but the clitoris was not hypertrophied and the external genitalia were otherwise normal. Residuals of the subcutaneous abscesses present early in the first admission were not detectable.

The thymus (2 Gm.), heart (18 Gm.), lungs (right, 25 Gm., left, 18 Gm.), alimentary tract, pancreas (6 Gm.), spleen (7 Gm.), adrenals (each 2 Gm.)

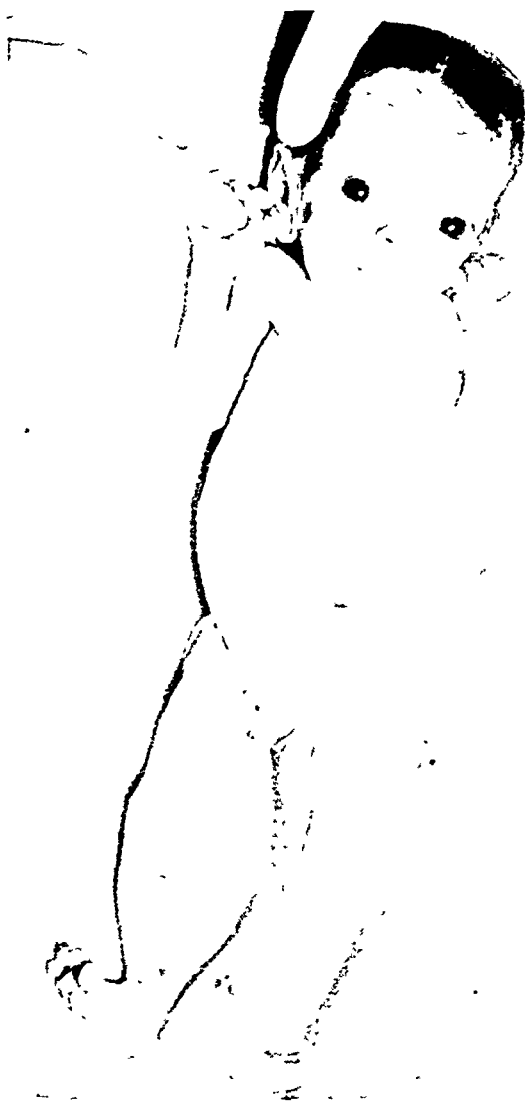


FIG. 1.



FIG. 2.

Figs 1 and 2.—Photographs of infant at 6 weeks of age. The emaciation, peculiar facies, large ears, and breast changes are well shown

were grossly not remarkable. However, all these organs were smaller than normal for a 7-week, full-term infant. This may be explained on the basis of the underdevelopment and emaciation. The liver was about half normal size (62 Gm.). It was of usual consistency, dark brownish red, and of normal contour. Scattered over the surface and throughout the substance of the liver were numerous small pale grayish yellow nodules measuring 2 to 3 cm. in diameter. These were flush with the surface of the liver. Grossly these were not unlike miliary tubercles. The gall bladder and bile ducts were normal.

Both kidneys were enlarged to approximately twice normal size, each weighing 36 Gm. They were brownish red, of normal contour, and there was no evidence of hydronephrosis. Their capsules stripped readily. The cut surface revealed cortex and medulla to be of normal relative width. The cortical markings were not blurred. The collecting tubules in the pyramids were streaked with deposits of grayish green material flecked with yellow. Both ovaries were tremendously enlarged, each measuring 3 cm. in the longest axis. In each were numerous cysts measuring up to 3 mm. in diameter. The uterus and tubes were slightly enlarged but otherwise appeared normal. The head and brain including the pituitary appeared normal.

Microscopically the following abnormalities were present: The lungs showed a moderate edema and an early bronchopneumonia. The picture in the liver was most interesting. Scattered throughout the parenchyma, having no relationship with either portal or central vein area, were sharply circumscribed patches in which the liver cells had undergone marked changes (Fig. 3). In these areas the liver cells were swollen, their cell boundaries indistinct, and in some places there had been fusion of 4 to 6 liver cells with clumping of the nuclei to form syncytial masses (Fig. 4). An additional change was extreme foamy vacuolization of the cytoplasm of the liver cells without displacement of the nuclei from a central position (Fig. 5). Differential stains revealed the presence of large amounts of glycogen in the cytoplasm of these foamy cells with minimal amounts in the relatively normal parts of the liver outside these focal areas. Fat was present in only minimal amounts, both in these foci and in other parts of the liver. Although jaundice was not obvious clinically or at post-mortem, many of the bile canaliculi in all parts of the liver tissue contained plugs of inspissated bile. There were heavy deposits of iron pigment in the liver cells and in the Kupffer cells in the intervening areas of the liver, but only a small amount was present in these peculiar focal areas. An interesting feature is the reciprocal relationship between the deposition of glycogen and iron pigment: much glycogen and practically no iron in the focal areas, and the reverse in the intervening liver tissue. The pancreas exhibited a tremendous increase in number and hyperplasia of the Islands of Langerhans (Figs. 6 and 7). No mitotic figures were seen in either the islet or acinar tissue. In respect to the islet tissue, differential stains revealed that beta cells were the predominating type, although the granulations in these appeared somewhat diminished. A similar alteration was not detected in the less numerous alpha cells. The ovaries showed a marked degree of follicular maturation without evidence of luteinization (Fig. 8). Most of the follicles showed ova in various stages of development (Fig. 9). Microscopically the uterus was not unusual. The breast tissue showed duct hyperplasia with early cyst formation (Fig. 10). Minimal histologic changes in the pituitary were difficult to appraise. Examination of this tissue gave the impression that there was a definite decrease in the number of basophiles, but those present appeared normal. The number of chromophobes and eosinophiles appeared to be within normal limits. Some of the eosinophiles showed depletion or exhaustion of their granules. No significant histologic changes were seen in the other endocrine glands. The adrenals were small, and the cortex was normal.

for the age of the infant. The thyroid was normal. Only one parathyroid was found. Histologically this was not unusual. Microscopically the kidneys exhibited diffuse dilatation of the tubules, particularly marked in the collecting tubules. Aside from this, no obvious cause was found for the large size of the kidneys. This dilatation was occasioned by conglomerate masses of a granular material plugging the collecting tubules (Fig. 11). This substance stains unevenly with hematoxylin. Differential stains showed these masses to contain a small amount of calcium. Iron was not present. Due to improper fixation, stains for urates were not done. The microscopic appearance of the other organs and the brain was within normal limits.



Fig. 2.—Photomicrograph (low power)—liver. The pale areas are the patchy foci of alteration in the liver cells.

The pathologic summary of this case is as follows: We have an extremely emaciated infant, who, although full term, had the body mass of a 7 to 8 months premature infant. The facies was peculiar, almost Negroid and there was evidence of aberration of the endocrine system as shown by changes in the ovaries, breasts, pancreas, and possibly the pituitary. In addition, peculiar focal changes were present in the liver, and there were calcified deposits in the collecting tubules of the kidneys, which indirectly may be related to the endocrine disturbances.

DR. A. L. CHUTE (Staff Physician).—It is unfortunate that this patient was not recognized as having endocrine dysfunction before autopsy. Otherwise more detailed metabolic studies would have been done.

The evidence of multiglandular changes at post-mortem would suggest that the pituitary gland, which is regarded as the regulator of the hormonal balance, was chiefly at fault in the present instance.

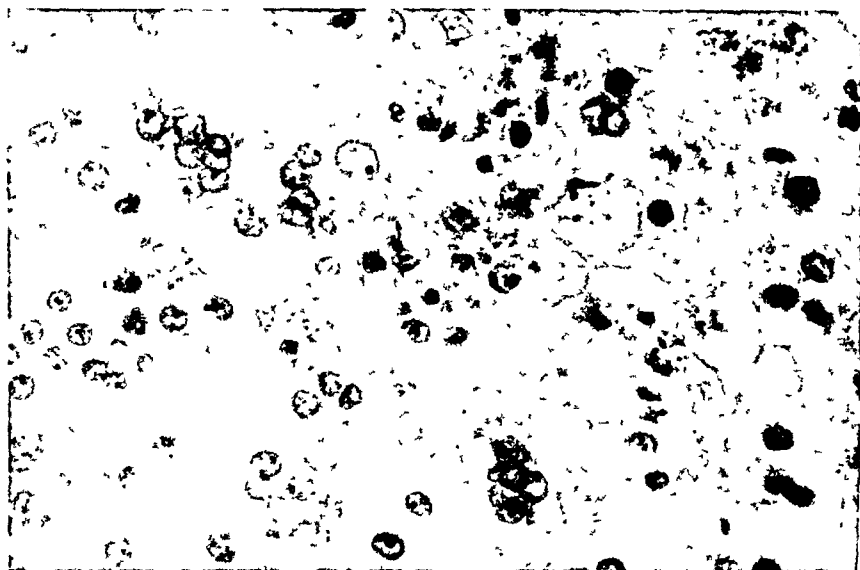


Fig. 4—Photomicrograph (high power)—liver. The center of one of the peculiar focal areas in the liver. The fusion of liver cells to form syncytial masses with clumping of the nuclei is shown.

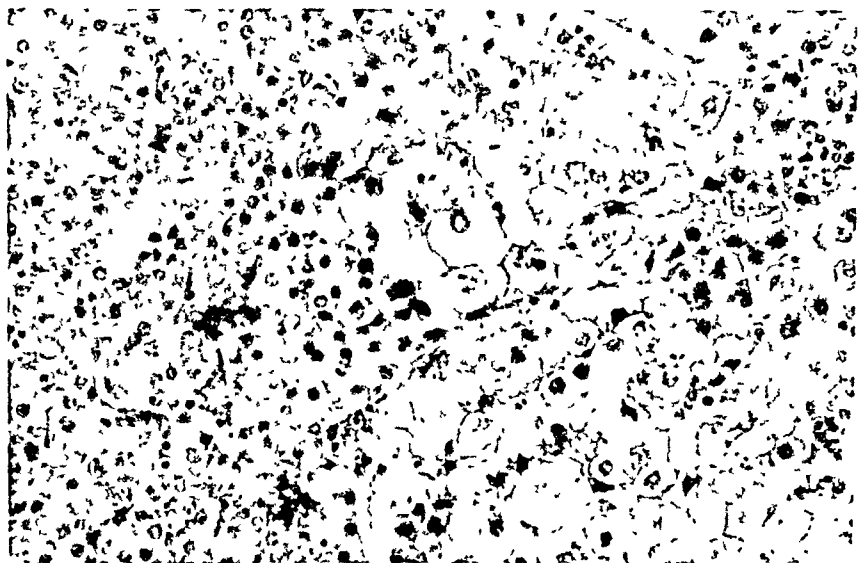


Fig. 5—Photomicrograph (medium power)—liver. Margin of one of the foci in the liver showing its sharp demarcation and the foamy vacuolated character of the cytoplasm of the liver cells in these areas.



Fig 6—Photomicrograph (medium power)—pancreas. The increase in number and size of the islets of Langerhans is obvious.

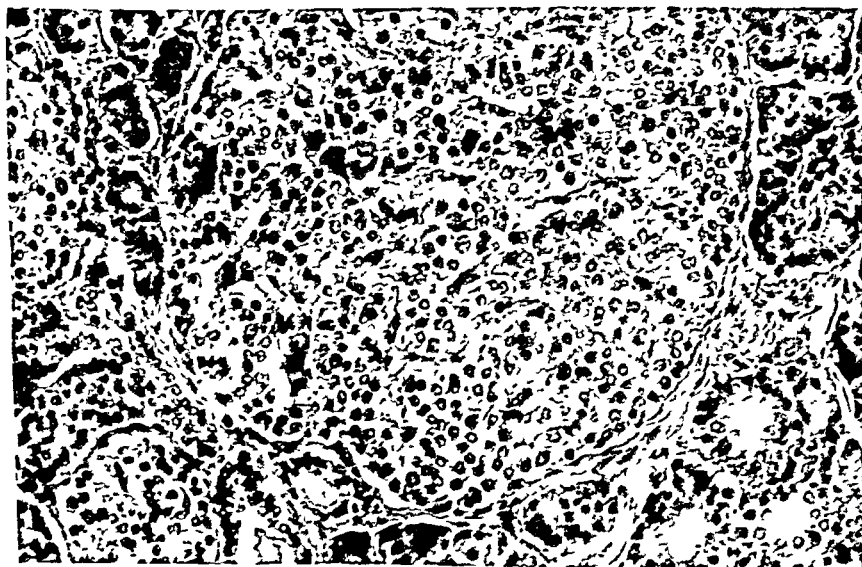


Fig 7—Photomicrograph (high power)—pancreas. This demonstrates the extreme hyperplasia of the islet tissue.

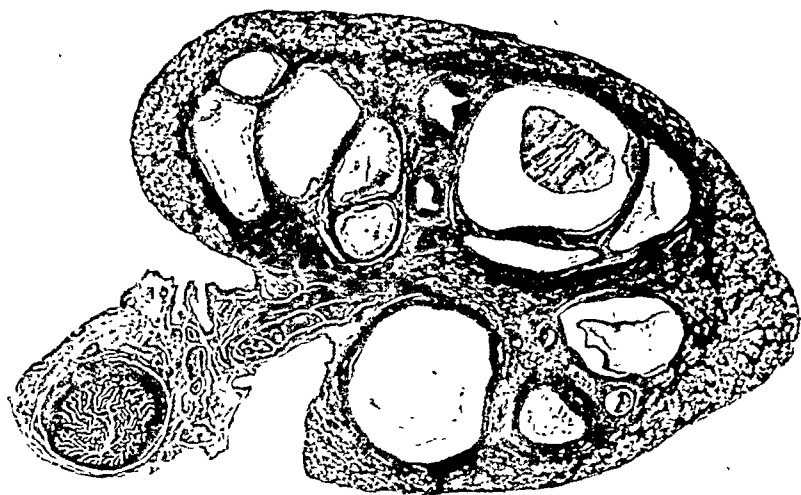


Fig. 8.—Photomicrograph (low power)—ovary. A cross section of ovary including the Fallopian tube. Note the large number of follicular cysts.



Fig. 9.—Photomicrograph (medium power)—ovary. In the center are two developing follicles, each containing an ovum.



Fig. 10.—Photomicrograph (low power)—breast. This shows the increase in the size of the ducts with hyperplasia of the duct epithelium and cyst formation. There is no evidence of developing acinar tissue.



Fig. 11.—Photomicrograph (medium power)—kidney. Deposits in the collecting tubules with resultant dilatation of these tubules.

Thus the enlarged ovaries with follicle formation suggest increase in gonadotropic activity. The enlarged breasts were secondary to the increase in ovarian function. Increase in the islet cells of the pancreas may have been brought about by anterior pituitary stimulation. Either this was so mild that it did not produce subsequent hydropic degeneration, or possibly the lower blood sugar of the fetus or insulin from the maternal circulation may have protected the islets from destruction. The focal deposits of glycogen in the liver suggest local enzyme abnormalities rather than endocrine dysfunction.

The enlarged kidneys with casts and calcium deposits point to parathyroid overactivity, which may be due, in turn, to pituitary stimulation.

Most of the changes so far described would suggest overfunction of the pituitary. The small size of this infant, however, suggests deficient growth hormone. This may be correlated with the finding of depletion or exhaustion of the granules in the eosinophiles of the pituitary. It is disappointing that with so many other glands affected the pituitary shows relatively little abnormality. Some of the changes, such as gonadal hypertrophy and hypertrichosis and possibly even the increase in islet cells of the pancreas, may be due to adrenal cortical overactivity. However, this gland also shows no pathologic changes.

The case is most interesting, but until our knowledge of the intricate interplay of endocrine activity has been perfected cases such as this remain an enigma.

DR. DONOHUE.—The question arises as to how we are going to classify this case. The standard textbooks of pediatrics and endocrinology were referred to, and we were unable to find an account of a similar syndrome. In consulting the *Cumulative Medical Index* we were confronted with the difficulty of establishing a title or adequate descriptive term under which to search. It is probable that similar cases have been reported, but we were unable to locate one. In our ignorance of the real nature of this process, we have, with a certain amount of cavil, classified this as a case of dysendocrinism.

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Psychologic Aspects of Pediatrics

ACCIDENT PRONENESS

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IN A recent paper, Press¹ called attention to the fact that in 1943 accidents were the leading cause of deaths in all children from 1 to 19 years of age. Even during the first year of life the death rate from accidents is considerable.

It has been conclusively shown that there are certain persons who are especially prone to have accidents. Insurance companies² have made the observation that mechanical hazards account for less than 10 per cent of industrial accidents, and physical and mental defects for only about 2 to 4 per cent of them. Eight per cent or less are related to lack of skill. This leaves about 80 per cent to be accounted for by something in the personality of the victim. More recent estimates indicate that this figure is more nearly 90 per cent, only about 10 per cent of accidents remaining which are purely "accidental." Even battle casualties are linked to the personality. A soldier who, as a civilian, has fallen down by accident and sustained an injury in the course of his normal routine at home or at work, is six times as likely to be permanently damaged in warfare as are others.³ The subject is of special importance to the pediatrician, not only because children as well as adults are accident-prone, but because, in addition, the characteristic personality pattern of the accident-prone adult is established during childhood in response to parental overauthority.⁴

The observation that there are individuals with an accident habit was first made by Marbe⁵ in 1926. In 1934 Alexander Adler⁶ suggested that an unknown factor in the human personality is responsible for the repetition of accidents in the same person.

Rawson⁷ analyzed the possible causes of accidents in four large industrial concerns employing 1,400 drivers of trucks and commercial vehicles. He found that, contrary to expectation, bad weather and defective roads played no part in causing accidents. Since all cars were inspected before they were taken out, defective equipment was not a factor; nor was speed, since 90 per cent of the cars had governors restricting speed to less than 45 miles per hour. All drivers had had from five to ten years of driving experience. Intensive education of the drivers and the imposition of severe penalties were of no avail.

Rawson's data showed that a relatively small number of individuals had a relatively large number of accidents. By the simple expedient of weeding out the repeaters the accident rate was reduced to one-fifth its original level. However, when the accident-prone drivers were transferred to other occupations, their accident habit continued. They no longer smashed up their cars, but they

injured themselves around the plant or at home. Repeaters tended to shorten the time between accidents.

Dunbar⁴ studied the personality patterns of a group of patients with fractures at the Presbyterian Hospital, New York. Her findings are, perhaps, all the more significant since she was unaware, at the beginning of her study, of the interest in accident proneness among industrial and insurance companies, and she intended to use the fracture patients as a "control" group for her observations on the personality patterns of patients with various diseases. She found the health record in this group to be exceptionally good, even to the point of freedom from colds and nervousness. They had had fewer major operations than any other group studied, and not many had had any type of major illness. They were relatively free from allergic disease, obesity, and poor teeth. Pelvic disorders were infrequent, and the venereal disease rate was low. The only minor illnesses at all frequent among them were gastrointestinal upsets.

In contrast with the excellent health record of these patients was the high incidence among them of previous accidents, including dislocation, fracture, severe burns, and bad cuts. Whereas 79 per cent of the patients with fractures had had two or more accidents, in none of the other groups of patients studied was there a similar history in more than 11 per cent.

The educational record of the patients with fractures was average although they showed a greater tendency than other groups to stop school before graduation from grammar school, high school, or college, as the case might be. In income and occupation the group did not differ materially from other groups.

As for general behavior the patients were usually of the happy-go-lucky type. They had few complaints but often showed a jerky, restless type of tension. They were well liked, talkative, and cheerful. Their sexual behavior was free from overt symptoms of conflict. They were casual about marriage and about extramarital affairs, and they were divorced or separated with relative ease. Their marriages were frequently childless or they had few children.

According to Dunbar, a prominent feature of accident-prone persons is impulsiveness. Their behavior is characterized by quick decisions and hurried activity. They concentrate on immediate pleasures rather than on long-term goals. They tend to be adventurous, like excitement, and prefer action. They like sports and are always in a hurry with plenty of time to spare. They develop strong emotional attachments to other persons. Despite their adventurous spirit they take very good care of their health.

Dunbar concludes, from a review of the histories of her fracture patients, that the outstanding feature in their development is conflict with authority, at first with parents or step-parents, then at school, later with church and employer, and finally in their marital relationships. Resistance to authority is particularly frequent in children who are brought up in a home where one or both parents are overauthoritative. Rejection is often associated with the overauthority. Accident-prone individuals have a good deal of pent-up aggression and resentment.

The revolt against overauthority manifests itself during childhood by restless behavior, lying, stealing, and truancy, but these tendencies disappear later

on. The personality pattern of the person with an accident habit resembles that of the juvenile delinquent and adult criminal—however, one breaks laws, the other breaks bones.³

Accident-prone persons are not awkward or clumsy, nor do they have poor coordination, low intelligence, or slow reaction time. In 80 to 90 per cent of the fracture patients studied by Dunbar some specific worry was reported preceding the accident. In many instances the patient was doing something he was not sure was right, such as disobeying a parent, attempting independent behavior, or avoiding authority. Frequently the patient expressed a feeling of guilt for behaving in this manner and said he deserved the accident: "It was really my fault because mother had said supper was ready and I was not to go out."⁴

The literature on accident proneness in children is meager. In a study of eighty-six children with severe head injuries, observed on the Children's Psychiatric Service, Bellevue Hospital, New York, Fabian and Bender⁵ found that thirty-three (38 per cent) had been involved in two or more major accidents and could be described as suffering from an accident habit. They believe that accidents in very young children, like temper tantrums, represent aggressive gestures which are turned against themselves, but are actually aimed at frustrating adults. It is common for children, when they feel that they are unfairly treated, to wish that they were sick or dead so that their parents will feel sorry for them. With the large majority of children, these ideas are transient and are not acted upon. However, some children do act out their fantasies, and then an "accident" may result.

Some children (and adults, too), when criticized or scolded or when they feel that they have been treated unjustly, obtain relief from pent-up aggression by striking inanimate objects, at times sustaining an injury in this way. Others, under similar circumstances, put themselves in dangerous situations. Jealous children sometimes inflict injuries on their younger siblings, especially when the younger sibling is rejected by the parents. A high percentage of accidents in children occur when they are doing things forbidden by their parents.

Fabian and Bender found psychopathologic disorders in the parents of 83 per cent of the children who had the accident habit. In half of these cases, one or both parents were alcoholic. In many instances the fathers were domineering, abusive, and rejecting, the mothers submissive and overprotecting. The fathers were shiftless and economically incapable. Violent display of temper was common. Marital disharmony, disruption of family life by hospitalization and jail sentences, as well as broken homes were common. The children were confused. Rejection, abuse, neglect intensified their aggressive drives.

When the person with an accident habit fails and can neither submit to nor avoid authority he is likely to do something about it. His aggression breaks out and he punishes himself and those responsible for his predicament without conscious plan or premeditation. Guilt and resentment are frequent reactions immediately following an accident.

Some children engage in habitual reckless play which brings repeated injury. They may have fear, unexpressed hatred, and guilt feelings. Injury causes the

child to receive attention and sympathy, but there are also indirect benefits, such as avoidance of disagreeable situations and evasion of responsibility. Hurting himself and thus relieving his sense of guilt is probably primary.⁹

Accidents are most common in young people. In Dunbar's fracture patients the group 15 to 24 years of age reported six times as many previous accidents as any other age group. The children studied by Fabian and Bender were 1 to 15 years of age. The highest number of accidents occurred in children 5 to 6 years of age. Ninety-two per cent of the children in their series were boys.

THERAPY

Accident proneness should be suspected in children who have frequent accidents or who have the personality make-up and home environment described in this paper. The accident habit should be looked upon as a "behavior problem," and efforts at correction should be directed toward improving conditions in the home and relieving the child of his feelings of guilt. Allowing the child to tell about his accident and what preceded it may bring out valuable information and, at the same time, help to free him of some of his doubts. Insight into the reason for the accident may help in preventing recurrences. Excessive coddling on the one hand or severity on the other hand should be avoided during the period of illness resulting from the injury, since these attitudes encourage impulsive behavior and delinquent tendencies.

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The Social Aspects of Medicine

NATIONAL HEALTH SERVICE IN GREAT BRITAIN

[Editor's Note: On page 217 of the February, 1948, issue we published a discussion by Evarts A. Graham, Jr., of the National Health Service plan for Great Britain, and of the proposed plebiscite of the medical profession by the British Medical Association. In an editorial in the April issue (page 478) the results of the plebiscite were given, which were overwhelmingly against the plan. The British government has stated it intends to inaugurate the service early in July despite the opposition of the medical profession. The broad and tolerant discussion of the existing situation by Dr. Alan Moncrieff which follows is not only timely, but we are sure it will help to a better understanding of the situation which confronts our British confreres, and in which the American doctors are so vitally interested.]

YOU asked me for some news of the National Health Service. The trouble is that things are changing fast, and this letter may be out of date by the time it reaches you. I must assume some knowledge on the part of your readers of the scope of the service. The article in the February issue of the JOURNAL OF PEDIATRICS was very good. It is a service for all—hospital, specialist, and general practitioner. Anyone can still get private service by paying, but everyone is entitled by right after July 5 to the whole service. Since the article by Evarts A. Graham, Jr., several things have happened of great importance.

A period of growing tension between government officials and the doctors preceded a plebiscite of the whole profession. This showed an overwhelming majority of doctors disapproving of the Act in its present form. This majority was not only among general practitioners but also among whole-time doctors already in government service and among whole-time research workers. It could be argued that doctors disapprove for varying reasons, but the fact is that 40,000 votes of confidence in the policy of resistance organized by the British Medical Association were recorded. While the plebiscite was in progress a debate was staged in the House of Commons, which was in itself a remarkable thing to happen. There had been some doubt cast upon the validity of the methods of vote-recording and secrecy, and the British Medical Association issued two writs for libel! But there is no question whatever but that the whole affair was conducted with the utmost rectitude. In the Parliamentary debate the Minister of Health Bevan indulged in some hard hitting, which no doubt pleased him and his supporters and for which he had had some provocation, but it certainly did no good and must have been in part responsible for the plebiscite result.

Another event is that a Gallup Poll showed that two-thirds of the general public thinks the Health Service a good idea, and about the same proportion claimed to understand the dispute between Bevan and the British Medical Association with a small majority showing sympathy with the doctors. This rather supports what happened in Parliament, where no political party was prepared to support the doctors' case in all its aspects. This case, which urges some amendment of the Act, has centered round four main difficulties and one referred to a special committee to be cleared up.

The four difficulties must be made plain. First comes the method of payment, which is determined by regulation and is not written into the Act. The Minister wants to pay all general practitioners a small basic salary (£ 300 per annum) and a capitation fee of less than £1 per patient on the doctor's list per annum. The British Medical Association does not want the basic salary, as being the first step to a whole-time salaried service. There does not seem to be any very good reason why the basic salary should be necessary or universal, and there is some hope that it may be withdrawn. Number two is concerned with the machinery for appeal to the courts against dismissal from the service. The Minister says that the various steps laid down in the Act give the doctor great safeguards and that he can go to the High Court under common law against illegal dismissal. The doctors seem to want a right to go to High Court on legal but unfair dismissal. It seems doubtful if this can be conceded, but psychologically something must be done to improve the appeal machinery. Third on the list comes the objection of the British Medical Association to any compulsion of doctors to work in any area. The Act indicates only what is called "negative direction"—that is, the power of the Minister to say that a doctor shall not work in an area which a local and a central committee of doctors have decided has too many doctors there already. This sounds all right, but the doctors do not like giving this power to the Minister. Fourth comes the question of buying and selling practices, which is abolished under the Act with a compensation scheme. This is probably not easily understood in the U. S. A. Over here a general practitioner buys the good will of a practice when he takes over. He pays a sum calculated to be about the equivalent of two years' income in return for an "introduction." This means that the outgoing doctor lets his patients know that he has disposed of his practice in this way to the new doctor, who therefore has every reason to suppose that the old patients will stick to him. The British Medical Association wants this retained because it gives the doctor some control over his practice and his successor. The general view in Parliament and elsewhere is against the retention of this curious transaction, which has the possibility of abuse even though it is usually only a harmless nuisance and gives the doctor a little bit of capital and something for his old age when he retires.

Now it is becoming doubtful if any of these four difficulties are any more than symbols of what the doctor regards as his "freedom." Specialists and general practitioners alike are increasingly worried that their professional freedom is at stake. They want assurances that they can continue to treat their patients to the best of their ability and without interference from the Minister of Health. They put forward these four points as being means of securing that freedom. But it is noteworthy that at the representative meeting of the British Medical Association just over, these four points were barely discussed. With great wisdom the Council of the British Medical Association and its chairman, Guy Dain, kept the meeting to a general resolution which asked for changes in the Act to preserve the integrity of medicine and prevent doctors from being made into State servants. It is perhaps not a tactful move when dealing with full-time civil servants to keep on saying that the last thing the doctor wants is to be made a full-time civil servant, but it certainly expresses the major fear of us all. What must be done is to devise some way in which the power of the Minister can be controlled so that no further changes in the direction of full-time salaried service can be made overnight, so to speak. So much of the Act is a framework with regulations to be devised by the Minister, and such regulations have the power of law without having to be fully debated in Parliament. Suggestions are being made as I write on how this point can be met. For example, some special procedure is possible within our constitution whereby all such regulations have to be examined by a special commission. Another scheme would

be to set up machinery for a standing committee from both sides which should discuss and even decide all matters of conditions of service and methods of payment. There is already in the Act a Central Health Services Council, which might play an important part. There is also a smaller committee under the Act which could be given greater powers in this field. However it is done, something must be done to restore the confidence of the doctors in the Minister—by curtailing his apparent overwhelming powers over them all.

Freedom to write on professional as well as scientific topics, freedom to criticize, and absolute freedom to work without lay interference or arm chair direction from administrative medical officers are the real demands which have led the doctors to reject the Act as it stands. To get it to work on July 5, which is the appointed day, will almost certainly need some form of amending legislation, and into this must be written some form of words which will secure such freedoms. It may be that such freedoms cannot really be guaranteed by Act of Parliament. Possibly the only long-term safeguard is for the doctors to make this service so good in its present form, with slight modifications, that no future Minister or Parliament will ever want to change it. Fears have been expressed that the Minister wants to be able to control the certification, which is an essential part of the new Social Security measures also coming into force on July 5. There will be no need for any such control if the doctors do such certifying in accordance with their traditions. But if it is badly done or even dishonestly done, then it will open the door to more rigorous control of the doctors than anyone will like. It is largely in our own hands.

The next few weeks will show how far the two sides can be persuaded to get together and work out not so much a compromise, because there cannot be a compromise where freedom or principles are concerned, but a means of safeguarding what the doctors hold most dearly. It cannot be said that the government has been very wise in the last few months. Even now it is obvious that great care should be taken to avoid provocation, and when, as said earlier, the British Medical Association Council has shown wisdom in preventing hothheaded action as a result of the plebiscite, the supporters of the government, in the shape of trade unions, have begun to threaten doctors in some areas as to what will happen if they do not agree to enter the service. You on the other side of the Atlantic should know very well what happens if you try to coerce a Britisher when he thinks freedom is involved. But there is still reason to hope that common sense will prevail, and by the time this is printed there may be signs of a settlement. These remarks will then be out of date, but they may serve as a background against which the agreement—not the victory of one or the other side—may be better understood.

ALAN MONCRIEFF.

In view of Dr. Moncrieff's discussion of the British National Health Service, some recent developments are of great interest. The information was obtained from the April 17 issue of *The Lancet*, which reached us in the mail on May 1.

On April 7, Mr. Bevan, Minister of Health, made a statement in the House of Commons regarding the attitude of the doctors to the National Health Service. Mr. Bevan stated that the key to the doctors' unease and restlessness was the fear that, although the Act did not propose it, the real objective was a full-time, salaried, State medical service. He then went on to say that something more than spoken assurance was needed, and in order to banish this apprehension he now wished to make it statutorily clear that a whole-time service would not be brought in by regulation but would require further legislation to be made possible. He further stated that the £300 salary would be made optional after the first three years. (The doctors could then choose plain capitation fees.) Another important point was the statement that there was no intention to interfere with

the ordinary rights of the doctors to express themselves in speech or writing with absolute freedom.

On April 8, the B.M.A. sent to the Minister fourteen questions, which he discussed with representatives of the Association on April 12. The questions with the Minister's replies appear in full in the April 17 issue of *The Lancet*, and discuss in more detail the points in Mr. Bevan's speech to the House. One of the questions was whether "freedom of speech and publication" extended to the right of criticism of the Act itself. The reply was that the statement included the right to publish views on the organization and administration of the service without obtaining prior consent.

The Lancet discusses the "Fourteen Points" editorially, and states that they understand a new plebiscite will be taken by the B.M.A. now that there are these new assurances. There are still some controversial points, but it would seem as if much of the controversy had been straightened out. *The Lancet* refers to Mr. Bevan's "genuine (and difficult) effort to secure happier relations with the profession." The "constructive questions" of the B.M.A. have "elicited reasonable answers." The editorial concludes: "We trust that the publication of these Fourteen Points will be quickly followed not merely by an armistice but by the common endeavor on which the good of the service so obviously depends."

The second plebiscite was taken, and early in May the result was announced. The profession was about equally divided between accepting and not accepting service, in contrast to the overwhelming opposition expressed in the first plebiscite. The newspapers published press dispatches on May 7, stating the B.M.A. as a result had withdrawn formal opposition as an association to the inauguration of the service in July.

B. S. V.

Comments on Current Literature

EXPERIMENTAL SERUM CARDITIS AND RHEUMATIC FEVER

RHEUMATIC infection is one of the chief causes of death in the school-age child and, likewise, one of the chief causes of disability in childhood and youth, producing cardiac damage that persists into adult life. Although in recent years considerable interest in this important problem has been aroused, the actual pathogenesis of rheumatic fever remains a mystery, and a satisfactory explanation of etiology has not been worked out thus far. The experimental work in animals is worthy of note. In animals rendered sensitive to foreign protein, lesions have been produced which resembled the lesions observed in the tissues of known rheumatic subjects.

Dr. E. Florence McKeown,¹ of the Institute of Pathology, Queens University, Belfast, has contributed an interesting report entitled "Experimental Serum Carditis and Its Relationship to Rheumatic Fever." In this paper McKeown includes a brief review of previous work indicating that the pathologic as well as the clinical manifestations of rheumatic fever may be on an allergic or hypersensitive basis. She points out that as early as 1902 Menzer² suggested that rheumatic fever results from the response in a predisposed individual to various microbes, especially streptococci. More recently, Vaubel³ (1932), Klinge⁴ (1933), and Junghans⁵ (1934) sensitized rabbits with small doses of horse serum and claim to have produced pathologic changes in the heart simulating the specific lesions of rheumatic fever. Aschoff⁶ (1935) denied that such experimental lesions duplicated the morphologic structure of the rheumatic nodule.

However, the conception that hypersensitivity plays a role in the pathogenesis of rheumatic fever has persisted. Recent observations by Rich and Gregory⁷ (1943) and Rich⁸ (1945) indicate that polyarteritis can be the result of sensitization. McKeown refers to the experimental work of Rich and Gregory and emphasizes the fact that in experimental polyarteritis nodosa, cardiac lesions were noted which histologically had many of the characteristics of the specific rheumatic granuloma. With this controversial situation in mind, McKeown undertook to verify and extend, if possible, the observations of Rich and Gregory. Horse serum was administered to two groups of rabbits, one group by intravenous route and one by intraperitoneal route. Careful observation of the rabbits revealed that cutaneous flushing accompanied by a rise in temperature was apparent on the twelfth to fourteenth day after injection. Skin tests performed at this time were positive. On the seventeenth day following the first injection of serum, all of the rabbits received one cubic centimeter of serum intravenously. Two days later the initial large dose of horse serum was repeated. The animals were killed at varying intervals following these injections and examined for the occurrence of pathologic lesions. The results of these experiments are striking and the report of the pathologic findings is extremely interesting.

Arterial lesions, which resembled closely the lesions seen in polyarteritis nodosa, were noted in 88 per cent of the experimental animals. Such vascular lesions resulted after the first injection of serum, but were more fulminant and widespread in animals receiving more than one injection. While arterial lesions were observed most commonly in the coronary system, evidence of arteritis was seen also in the other vessels studied. Changes in the coronary arteries were striking, the entire coronary system being affected. Early pathologic changes noted were edema of the media, swelling of muscle fibers, and loss of nuclear

definition. The arterial walls were swollen and homogeneous, and the lumina reduced in size. There was definite perivascular edema. These early changes were followed by inflammatory infiltration and fibrinoid necrosis of the vessel walls. Polymorphonuclear leucocytes and eosinophiles were noted in large numbers in the adventitia of the coronary blood vessels. Somewhat later, large mononuclear cells were seen. Observations made after sufficient periods revealed that healing takes place in these animals by fibrous replacement of the necrotic muscle, proceeding finally to complete healing. In certain instances primary damage, which had resulted in almost complete medial fibrosis and thickening of the adventitia, had become the site of an acute inflammatory reaction superimposed on the old lesion. These changes in the coronary blood vessels were accompanied by extensive myocardial fibrosis. The description of myocardial Aschofflike lesions is of interest. These were seen in the adventitia of blood vessels most commonly associated with vascular lesions, but were seen also quite frequently in relation to a vessel which showed no damage to media or intima.

Judging by these descriptions, the nodules must bear a close resemblance to the Aschoff nodules considered characteristic of rheumatic fever. The excellent verbal description given by McKeown is supplemented by good photographs of the pathologic lesions. The author points out that while the nodule produced bears a close resemblance to the Aschoff nodule of rheumatic fever and seems to pass through a similar evolution, the end result of the experimental process was paravascular scarring, which is not of the fibrillar type found in rheumatic fever.

Changes in the endocardium were notable, again the earliest change being necrosis of collagen. The fully developed endocardial lesion was an Aschofflike nodule similar to that described in the myocardium. Another endocardial lesion was observed which resembled that seen in rheumatic endocarditis. Palisades of proliferating cells were seen overlying the subendothelial bands of necrotic collagen.

The cardiac valves also showed interesting changes. Lesions of the mitral valve, valve rings, and angles were often present even in the absence of myocardial changes. The response in the aortic and tricuspid valves was similar, but these were involved less frequently. The pulmonary valves showed no specific lesions. Edema of the connective tissue of the valve rings was followed by increased vascularity and diffuse inflammatory infiltration. In more specific lesions large mononuclear cells of the Aschoff type were present. As the inflammatory reaction subsided, healing took place with the formation of a loose cellular fibrous tissue, which later became hyalinized. Changes noted in the valve itself seemed quite characteristic of the Aschoff type of response. When the Aschofflike nodule occurred near the surface of the valve, proliferative changes were observed in the overlying endocardium, the endothelium becoming elevated by large numbers of inflammatory and large mononuclear cells arranged in a palisade at right angles to the underlying zone of damaged collagen. Eventually healing of the valvular lesions occurred with vascularization and fibrosis.

In addition to these lesions noted in the heart, vascular lesions were reported in the lungs, liver, and spleen, those in the liver being identical with the lesions occurring in polyarteritis nodosa.

In the discussion, McKeown summarizes the characteristics of this type of lesion observed in rabbits sensitized by a bland nontoxic protein. The earliest lesion in the heart appears to be a focal necrosis of collagen, associated with an inflammatory reaction. These experimentally produced lesions are compared with those reported by the author in 1945⁹ in studies of human material. She points out that the lesions seen in human subjects with the rheumatic process are similar in many respects to those produced in experimental animals, and con-

cludes that "In histological structure and in site the experimental lesion is identical with the specific granuloma of the naturally occurring disease." The analogy is supported further by the fact that the endocardial and valvular lesions are of similar nature, and analysis of these valvular lesions shows their close identity with those of rheumatic valvulitis: the frequent involvement of mitral valves, the focal nature of the initial lesion, and the similarity in type of reaction. Endocardial lesions in the left auricle were seen in the experimental animal as well as in the human subject.

The most striking parallel between the conditions observed in the experimental animal and in the rheumatic subject is to be found in the fact that in both the mitral valve is involved most frequently, whereas the pulmonary valve shows practically no changes in either the experimental animal or in the human subject. Changes in the coronary arteries were thought to be similar in the human material and in the experimentally hypersensitized rabbit. Of considerable interest were the changes noted during the healing process, which in many respects resemble the healing process noted in the human subject. McKeown concludes that "these analogies in site and quality of the lesion strongly suggest that hypersensitivity is the essential mechanism in the production of the rheumatic lesion," and states that while bacteria or their products, especially hemolytic streptococci, are probably the basis for hypersensitivity in the rheumatic subject, so far as she is aware experimental animals have not been sensitized by intravenous doses of killed hemolytic streptococci. Certain clinical and serologic observations would seem to incriminate hemolytic streptococcus, and in conclusion, McKeown states, "While there is no clear indication as to the causal factor responsible for sensitization, it is suggested on clinical grounds that the hemolytic streptococcus is more closely allied to rheumatic fever than any other organism and that hypersensitivity is probably the result of bacterial sensitization, possibly of streptococcal origin."

RUSSELL J. BLATTNER.

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Correspondence

EXSANGUINATION TRANSFUSION IN A NEWBORN INFANT IN 1925

[Editor's Note: A few weeks ago our attention was called to a case report published in 1925 in which an exsanguination transfusion in a 3-day-old infant was performed for what was obviously what is now known as erythroblastosis fetalis. Through Dr. Alan Brown of Toronto, Dr. Alfred P. Hart of Toronto, who had reported the case, has kindly sent us the following information.]

April 24, 1948

Dear Dr. Veeder:

As requested by Dr. Alan Brown, I am writing to call your attention to an article on "Familial Icterus Gravis of the New-Born" and its treatment, published by me in the *Canadian Medical Association Journal* 15: 1008-11, 1925.

The case which occasioned this article was that of a male child born on Dec. 18, 1924. The parents had had seven children born previously which all had appeared healthy and vigorous at birth, but had all developed jaundice within the first twenty-four hours. This had become progressively worse until death had occurred in from three to eleven days, in all except the second child, a girl, who had been jaundiced as the others, but had managed to live although deeply jaundiced until one year old and weighing at this age only what she had done at birth. She was still living and normal. The eighth child, whom I was called to see, was a vigorous healthy baby. On the second day jaundice appeared which by the third day had become so intense that the skin was deep orange in colour. The blood examination as we knew it at that time was normal. We had no knowledge of the Rh factor. We could find nothing in the literature to help us in the treatment. Feeling that there was some toxin circulating in the blood and that if something drastic was not done at once the child was certainly going to die as the six other previous male babies had done, it was decided to do an exsanguination transfusion after the technique brought out and perfected by the late Dr. Bruce Robertson, in the hope of removing sufficient toxin to prevent the progress of the disease. The baby was in Group 11 jansky.

Dr. J. L. MacDonald of the Hospital for Sick Children exsanguinated 300 c.c. of blood from the anterior fontanelle, at the same time transfusing 335 c.c. of blood into the internal saphenous vein at the left ankle. The transfusion of blood was commenced after 20 c.c. of blood had been exsanguinated, and the transfusion and exsanguination went on synchronously until the required quantity had been used, and we ended by giving the baby 35 c.c. more than had been removed. In addition, 60 c.c. of 5 per cent glucose solution were given. The donor was a healthy male not belonging to the family. By the following morning the jaundice was much less intense. It continued to fade so that by the fourth day it had entirely disappeared. He had a slight return of jaundice when 3 weeks old, but afterward developed as a normal healthy baby. He is now a big man, over six feet, and healthy. He is a butcher, and has one child.

Although we did not know these cases as erythroblastosis foetalis in those days, I believe that this case was actually the first case in which exsanguination transfusion was used in this condition. Possibly for the sake of the history of medicine, one might be justified in bringing this to the attention of the profession.

Thanking you, I remain,

Yours very truly,
(Signed) ALFRED P. HART.

News and Notes

The Rocky Mountain Pediatric Society has elected the following officers for 1948: President, Dr. John M. Nelson; Vice-president, Dr. Galen C. Garvin; Secretary-treasurer, Dr. Edwin T. Williams. Monthly meetings are held at the Children's Hospital or the Colorado General Hospital except during the months of July, August, and September.

Dr. Thomas Parran, former chief of the U. S. Public Health Service, is head of a mission to study the extension of services to mothers and children in the Far East (Philippines, Indo-China, Ceylon, etc.) by the United Nations International Children's Emergency Fund. The fund now has a feeding program for nearly four million children in twelve European countries. A mass vaccination program against tuberculosis in children in Europe will be undertaken with B.C.G. The work will be largely undertaken by Scandinavian personnel under Dr. Holm of Denmark. Children in Germany will now be aided by the fund if requests are made by the zonal commanders. The fund is supported by government grants, and a campaign is under way to raise \$60,000,000 from private gifts in the United States.

The University of California Medical School offers a postgraduate course in pediatrics June 28 through July 2, at the University of California Hospital in San Francisco. Hours will be from 9 A.M. to 5 P.M. for the five days. The staff consists of seventeen members of the pediatric and related departments of the medical school. It will cover infant feeding, blood dyscrasias, poliomyelitis, allergy, tuberculosis, chemotherapy, rheumatic fever, etc. The fee is \$50.00. For details, address Dr. Stacy R. Mettler, University of California Medical Center, San Francisco 22, Calif.

The following were certified by the American Board of Pediatrics at the examination in Cleveland, April 23-25, 1948:

- Dr. Alfred B. Amler, 62 Greenridge Avenue, White Plains, N. Y.
- Dr. Raymond Burk Anderson, Plaza Time Bldg., 411 Alameda Rd., Kansas City, Mo.
- Dr. Emanuel Berger, 1745 North 4th Street, Philadelphia, Pa.
- Dr. Abraham Berkow, M.D., 417 West Main Street, Hackensack, N. J.
- Dr. Benjamin Clemens Berlinger, 163 East Rockaway Road, Hewlett Harbor, N. Y.
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Dr. James Alexander Wolff, Children's Hospital, Boston 15, Mass.

Book Reviews

Diseases of Children's Eyes. J. H. Doggart, F.R.C.S., St. Louis, 1947, C. V. Mosby Co., 288 pages. Price \$10.00.

This is an excellent text by a British ophthalmologist on the eye diseases as they are found in children. The material comes largely from the Great Ormond Street Hospital. While it contains nothing not found in the larger complete texts on ophthalmology, the compiling of the conditions common to or seen in children makes it of unusual value to the pediatrician and to pediatric clinics. The text is beautifully illustrated, and a large part of the 218 illustrations are in color. There are thirty-two color plates in addition to the text, illustrating lesions of the fundus, cataracts, and corneal and external diseases.

Give Your Child a Chance. Lenore Turner, New York, 1946, The Georgian Press, pp. 171. Price \$1.50.

This new and comparatively short book for parents on child training is in many respects outstanding in its field. Except for a chapter on feeding, it is chiefly concerned with emotional health. The author has succeeded in presenting a readable text of present-day thought in nontechnical terms, which should be of great help to parents. The chapters on toilet training and sex education are unusually good and sane. In view of the scarcity of good nursery schools and of competent nursery school teachers, we cannot share the author's enthusiasm for the nursery school. We do not differ with the ideals the author has in mind, but a poor nursery school is worse than none, and the pediatrician's approach to the nursery school must be pragmatic. The book has short prefaces by Drs. Donovan McCune and Norvelle C. LaMar. It is a book that the reviewer has added to his list to recommend to parents and one he feels with which the pediatrician should become familiar.

B. S. V.

How to Help Your Child Grow Up. Angelo Patri, Chicago, 1948, Rand McNally Co., pp. 352. Price \$4.00.

For many years the author has had a syndicated column in the newspapers on child care and training, which has been regarded by many pediatricians as perhaps the most sane and sensible of its kind. The present volume is compiled and arranged from these articles. It is intelligible reading for the average parent.

Melk. In *Het Bijzonder Als Zuigelingenvoedsel*. J. H. De Haas and Ir. O. Meulemans, Batavia, 1947, ed. 2.

A monograph on milk and its use in infant feeding.

Editor's Column

THE 1946 INFANT MORTALITY RATE

FIGURES recently released by the Bureau of Vital Statistics show that the steady decline of the last thirty years in the I M R is continuing. The rate for 1946 for the United States as a whole was 33.8, or 11.7 per cent under the 38.3 rate for 1945. In 1941, the rate was 45.3, which makes a 25 per cent decrease in the last five years. There were 6,379 more deaths in 1946 than in 1945, but a tremendous increase in births took place in 1946.

Marked differences, as usual, exist in the I M R by states. Utah, with 27.2, had the lowest rate in 1946, and New Mexico, with 78.2, the highest. Too much importance cannot be attached to the state rates for comparative purposes, as in states with a low birth rate small differences in the number of deaths will lead to relatively large differences in the I M R.

Of the 111,063 infant deaths which occurred in 1946, almost three-fourths took place within the first month. Almost exactly a third (33.9 per cent) occurred in the first twenty-four hours after birth.

Premature birth remained the leading cause of death, accounting for 12.1 of the 33.8 rate. The diarrheal diseases, which formerly were so important, were responsible for only 1.7 (5 per cent) of the total deaths. Whooping cough remains the chief cause of deaths among the infectious diseases but furnished only 0.3 of the total rate.

The rates for the states with the largest number of births were as follows:

	1946	1945
New York	29.1	31.8
Pennsylvania	33.0	37.9
California	30.7	32.5
Texas	41.7	48.8
Illinois	30.4	31.6

Credit must be given to the states with the highest rates for a marked improvement in the 1946 rate compared with 1945:

	1946	1945
New Mexico	78.2	100.8
Arizona	41.5	68.7
West Virginia	40.9	52.0
Colorado	40.0	50.5

B. S. V.

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND
DISEASES OF INFANCY AND CHILDHOOD

Editor

BORDEN S. VEEDER
St. Louis

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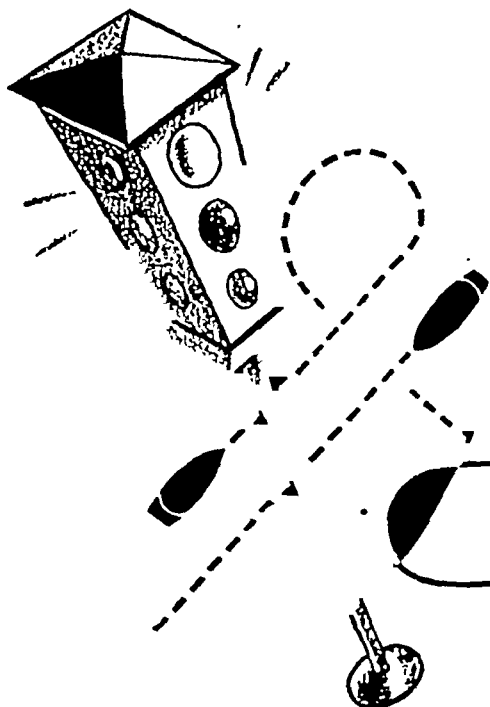


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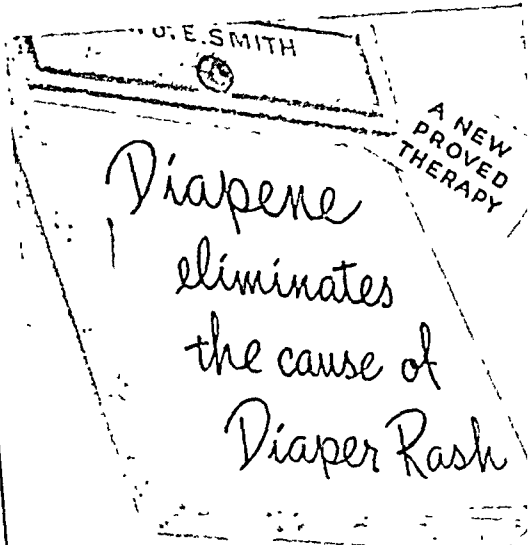


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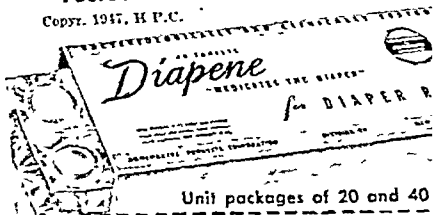
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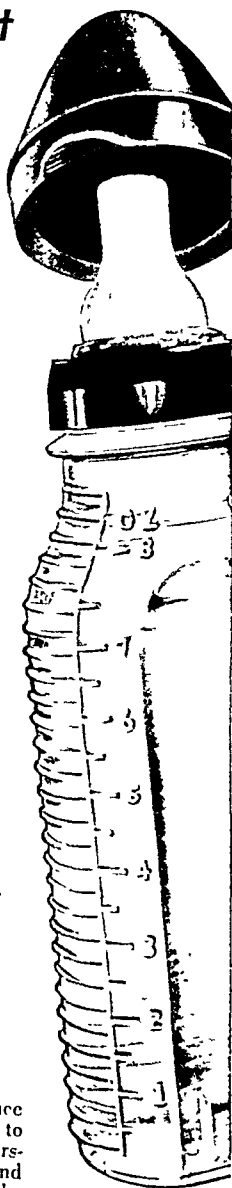
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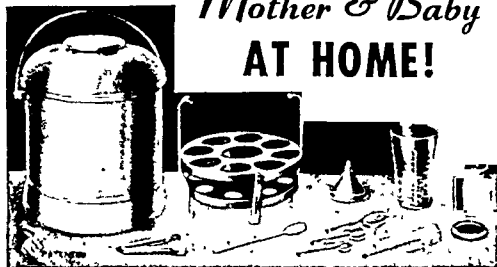
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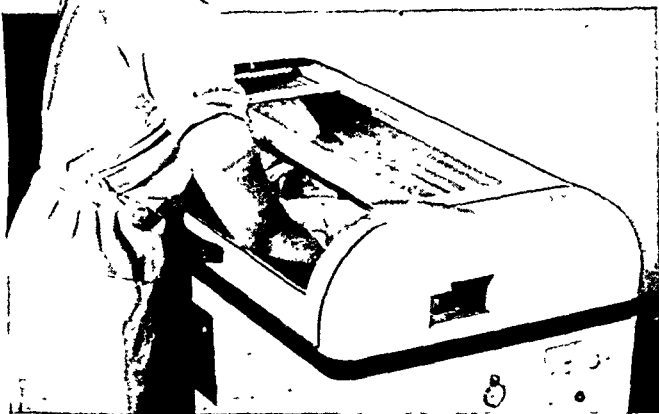
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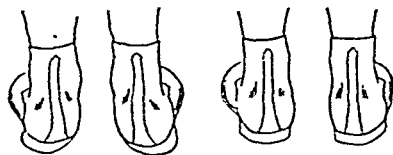
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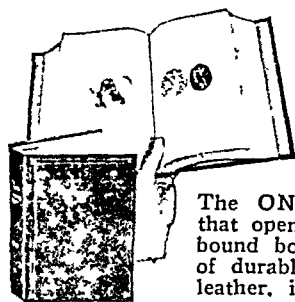
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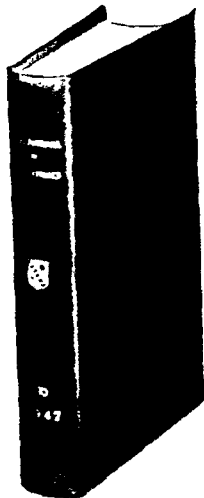
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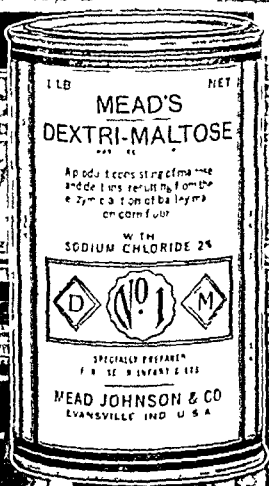
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BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



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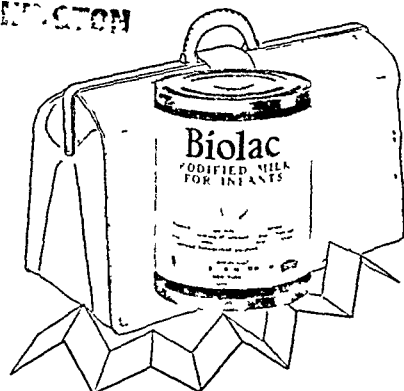
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UNIVERSITY OF WASHINGTON

put Summer Safety in your formula prescription



Adding cooled boiled water to BIOLAC—as her physician directs—is the only precaution that a vacation-minded mother need take when preparing her infant's formula during the summer months. This simple procedure not only facilitates formula preparation, but also minimizes the possibilities either of contamination under adverse travel or resort conditions, or the chance omission of needed vitamins, carbohydrates or iron. BIOLAC, when supplemented by vitamin C, is a complete infant food. In readily assimilable form, it dependably provides all the essential proteins, vitamins, minerals, carbohydrates and other nutritional factors needed for optimum health.

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1 fl oz Biolac to
1½ fl oz water per
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Vol. 32

MAY, 1948

MAY 26 1948

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CHILD HEALTH CENTER
UNIVERSITY OF WASHINGTON

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

Editor

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St. Louis

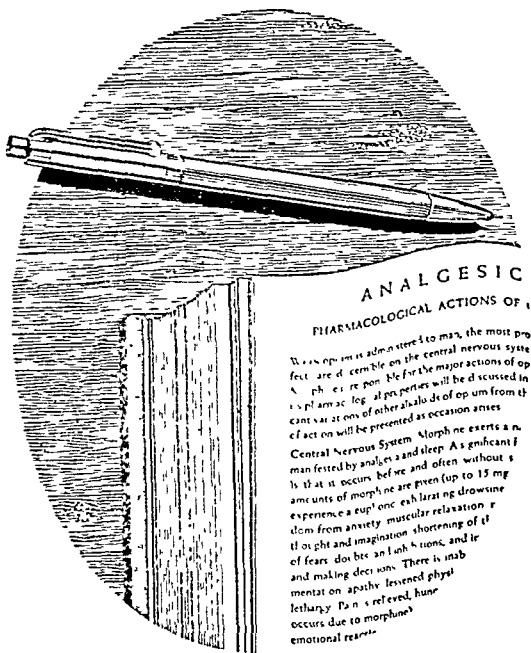
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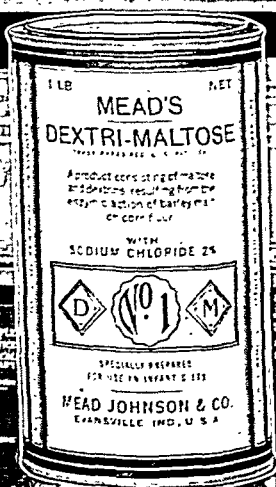
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BACKGROUND

The use of cow's milk, water and carbohydrate mixtures represents the one system of

infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextri-Maltose.

What every doctor knows:

SUPERIOR DIET BUILDS SUPERIOR CHILDREN

*Excerpts from
"INFANT NUTRITION"*

by

P. C. Jeans, A.B., M.D. and Williams McKim Marriott, B.S., M.D.

The C. V. Mosby Company

Fourth Edition 1947

- Nutrition is by far the most important of the controllable factors that determine the rate of growth of the normal infant . . .
- Fully adequate nutrition permits optimum growth . . . Page 17
- . . . the well-fed baby will usually grow at a rate somewhat greater than the average for his birth length. Page 22
- A baby who is given a proper diet and is gaining well is usually thriving in all other respects. Page 23
- Well-nourished children tend to erupt their teeth somewhat earlier than average . . . Page 27
- Growth in length is due entirely to growth of the skeleton; bone growth, in turn, depends on the nutritional status and on heredity . . . Page 31

Campbell's meat-and-vegetable Baby Foods —an aid in building superior diet

Here are four highly nourishing meat-and-vegetable foods: Chicken . . . Beef . . . Lamb . . . Liver. In addition to meat, each food contains from 5 to 7 of the most valuable vegetables, and a cereal. The green and yellow vegetables included are known to contribute important dietary essentials. Each of the four foods is a nutritionally proportioned meat-and-vegetable main dish for a baby's meal.

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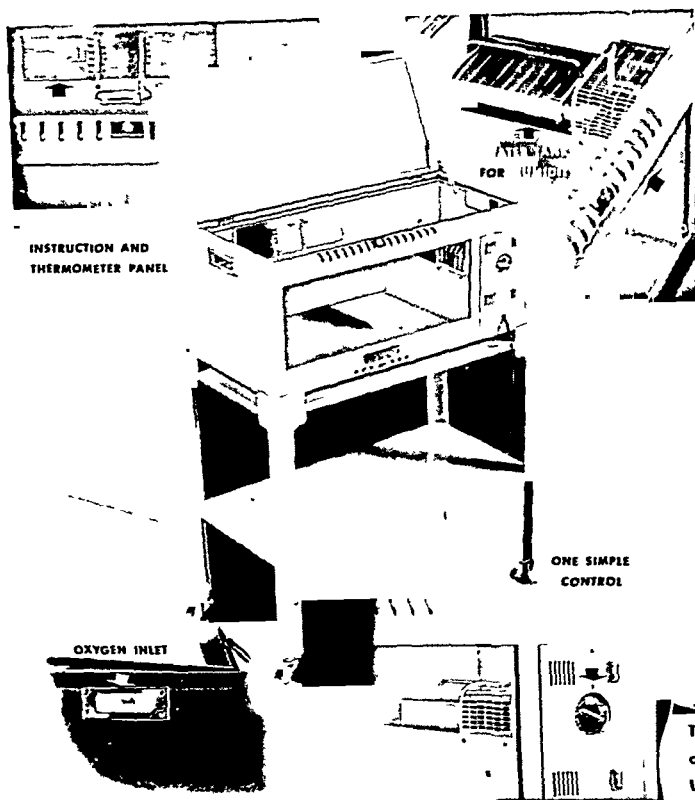
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LAMB	+ 5 VEGETABLES + BARLEY
LIVER	+ 7 VEGETABLES + OATMEAL
VEGETABLE	= 8 VEGETABLES + OATMEAL

*Dietetic analyses of these strained foods
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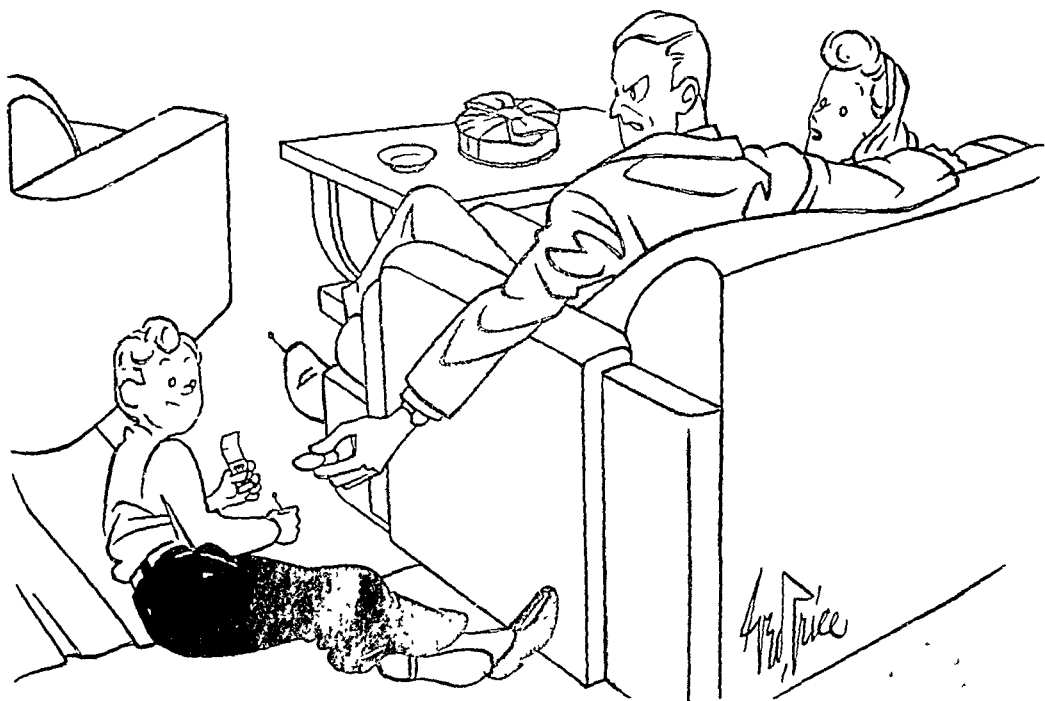
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Riboflavin	1.2 mg.
Nicotinamide	10 mg.

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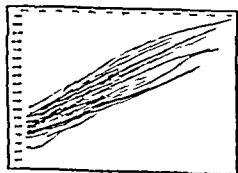


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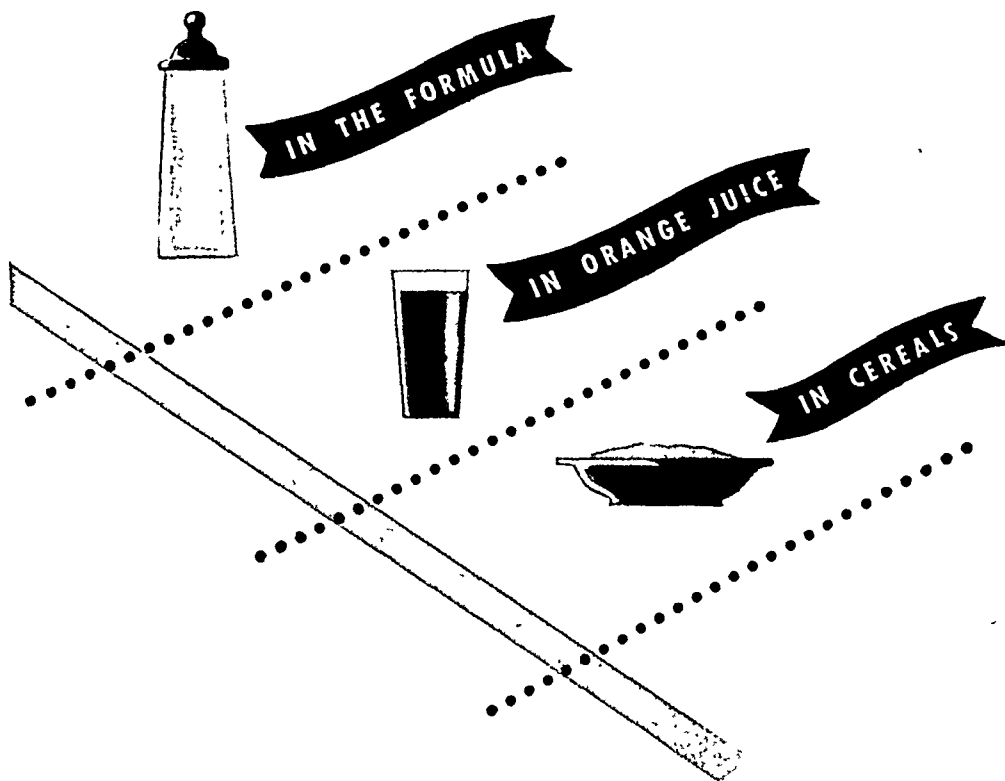


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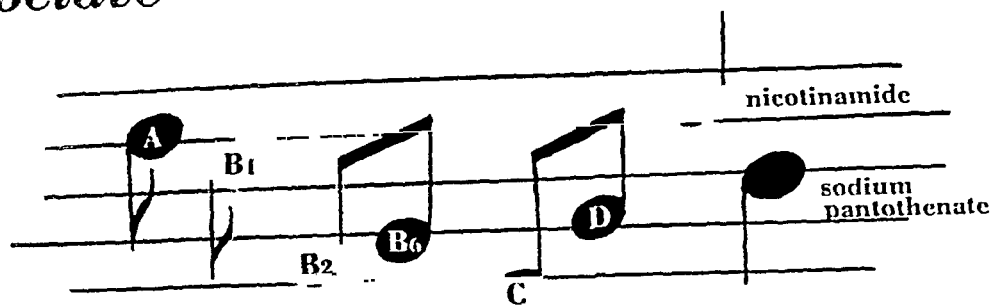
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“octave”



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when you prescribe*

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1 Soper, H W Am J Digest Dis 11 255 (1944)

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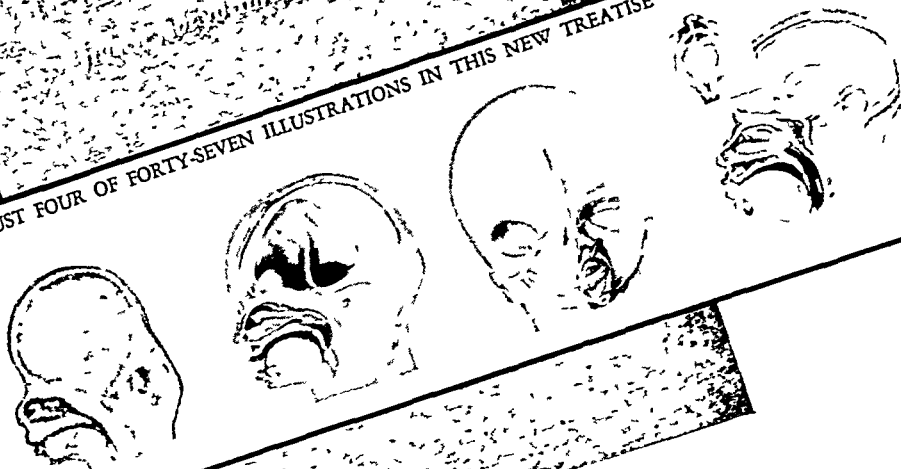
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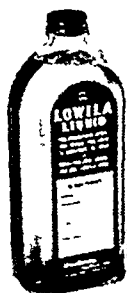
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**non-irritant
lathering
detergents**

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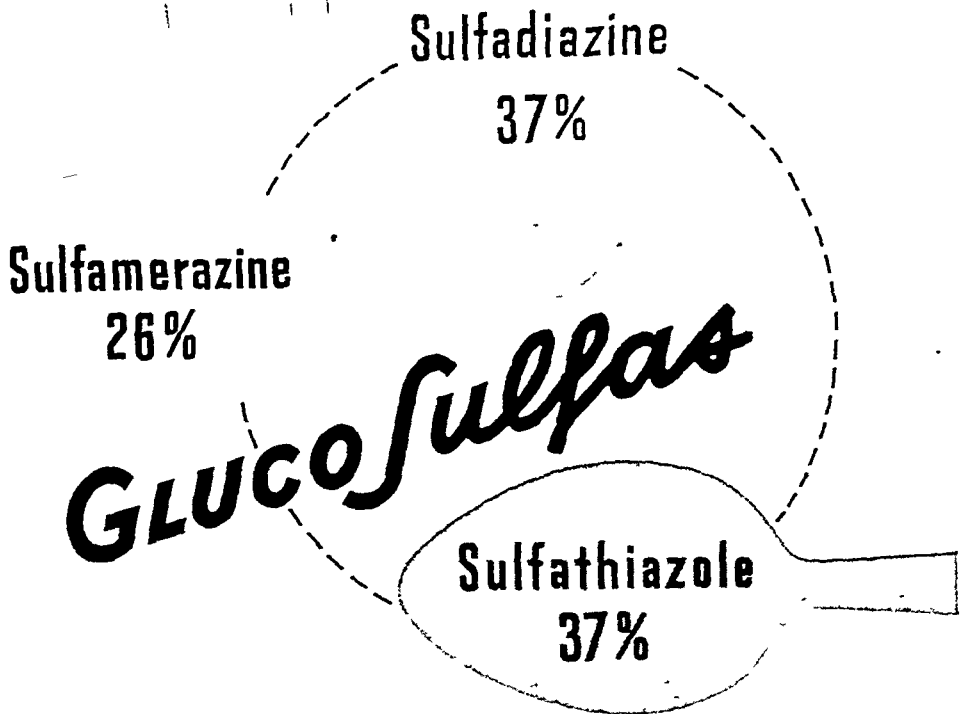
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
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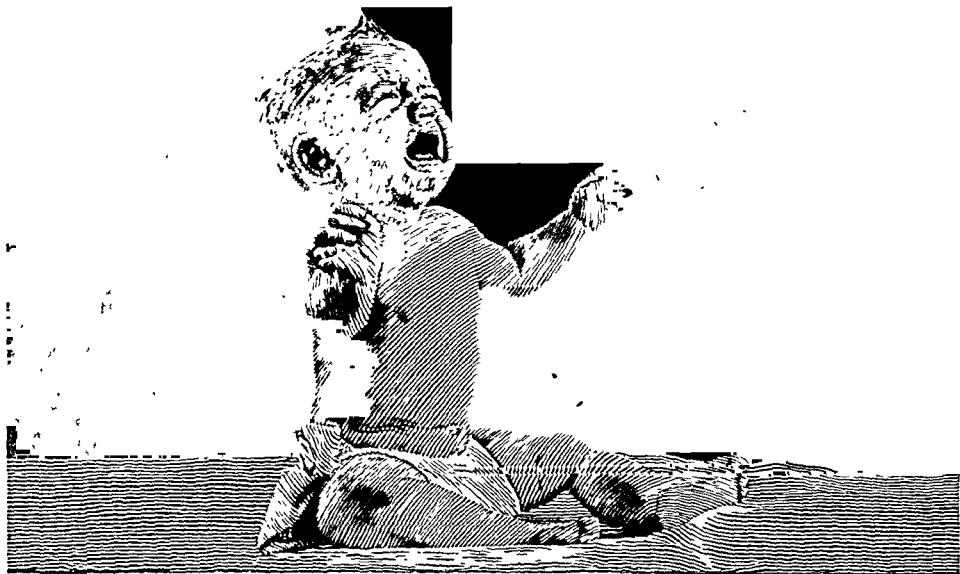
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¹ Frisk, A. R., et al. British Med J 1 7-10 (Jan 4), 1947.

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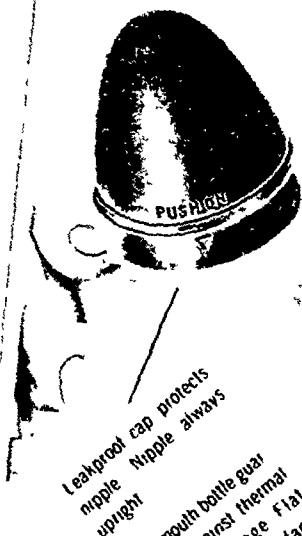
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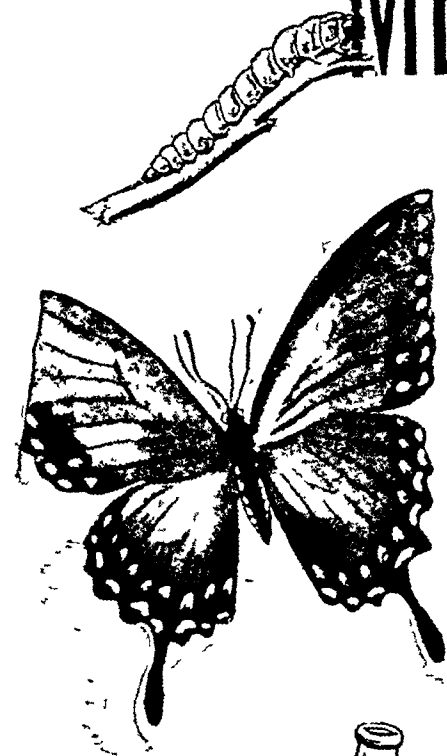


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METAMORPHOSIS of Milk



Rennet-custards are visually more attractive by virtue of their diversity of colors and toppings . . . more tempting to the palate because of their flavors and consistency . . . and digestively more acceptable than unmodified cow's milk because of their smaller, more friable curds.

In infancy and childhood, in certain gastro-intestinal diseases, in pregnancy and lactation and for geriatric patients, milk is a dietary "must". However, because of the patient's aversion or intolerance, it often proves inadvisable to insist upon the ingestion of an adequate intake of unmodified cow's milk in the usual liquid form.

In such cases, the metamorphosis of milk into delicious rennet-custards (quickly and easily prepared either from "Junket" Rennet Powder or "Junket" Rennet Tablets) has been found a highly welcome solution of the problem—from both a psychologic as well as physiologic point of view.

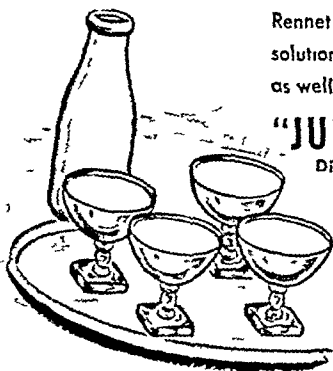
"JUNKET" BRAND FOODS

Division of Chr. Hansen's Laboratory, Inc.

LITTLE FALLS, N. Y.

B-55

"JUNKET" is the trade-mark Chr. Hansen's Laboratory, Inc., for its rennet and other products, and is registered in the U.S. and Canada.



MAKE RENNET-CUSTARDS WITH EITHER

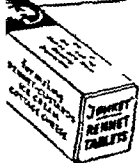
"JUNKET" RENNET POWDER

— six popular flavors,
already sweetened;

"JUNKET" RENNET TABLETS

— not sweetened or
flavored—add sugar
and flavor to taste

A series of four
authoritative,
time saving in-
fants' and chil-
dren's diet lists
are available to
physicians on re-
quest without cost
or obligation.





DONNATAL **tablets** **or...**

*-for effective
spasmodysis*

DONNATAL—a synergistic combination of the principal belladonna alkaloids in fixed amounts, with a minimal sedative dose of phenobarbital—has long been known in tablet form, for its gentle, non-toxic, non-narcotic relief in smooth muscle spasm.

And with the introduction of Donnatal Elixir, the range of clinical usefulness of this safe, dependable spasmolytic has been considerably extended.

Donnatal Elixir features with unique success the three essentials of oral medication: high palatability, ease of administration, and flexibility of dosage.

INDICATIONS: *Tablets*—Disorders of spastic origin in gastrointestinal, biliary, urogenital and respiratory tracts.

Elixir—Spastic pyloric stenosis, intestinal colic, diarrhea, enuresis.

FORMULA: Each teaspoonful (5 cc.) of Elixir and each Tablet of Donnatal contain:

Hyoscyamine Sulfate	0.1037 mg.
Atropine Sulfate	0.0194 mg.
Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital ($\frac{1}{4}$ gr.)	16.2 mg.

AVAILABLE: Elixir in pint and gallon bottles; Tablets in bottles of 100, 500 and 1000.

A. H. ROBINS COMPANY
RICHMOND 20, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878.

*-as each case
may require*

DONNATAL 'Robins'
Tablets or Elixir

Swift's Strained Meats

checked drop in hemoglobin

typical of early infancy

Six-weeks-old infants who received Swift's Strained Meats, in recent feeding tests, had higher hemoglobin level and better red cell values than infants on the meatless formula. Results showed the average hemoglobin and red cell values of meat-fed infants were 113.3% and 122.2%, respectively, of the average values at the beginning of the study. Values for the control group were 89.7% and 106.2%. As demonstrated by this study, meat actually checked the drop in hemoglobin characteristic of infants at this age.

The study further revealed that when infants' protein intake was increased 25% by the addition of Swift's Strained Meats to their formula, they slept better, were more satisfied, and in a better physical condition generally.



Specially prepared 100% meats for earlier meat-feeding. Swift's Strained Meats—fine enough for formula-feeding—facilitate introducing meat *earlier in life*. An excellent, palatable source of complete, high-quality proteins, Swift's Strained Meats also furnish goodly amounts of thiamine, niacin, riboflavin and iron—nutrients not ordinarily plentiful in the infant diet. Swift's Strained Meats offer six distinctive flavors: beef, lamb, pork, veal, liver and heart. Each one all meat, not a mixture. The tempting variety helps baby form sound eating habits. For further information, write Dept. SMB, Swift & Company, Chicago 9, Illinois.



SWIFT

...foremost name in meats

first with 100% Meats for Babies



All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association

ALSO SWIFT'S DICED MEATS

Tender, bite size bits of meat—firm enough to encourage chewing. Six flavorful kinds of Swift's Diced Meats help prevent anorexia in the older baby and young child

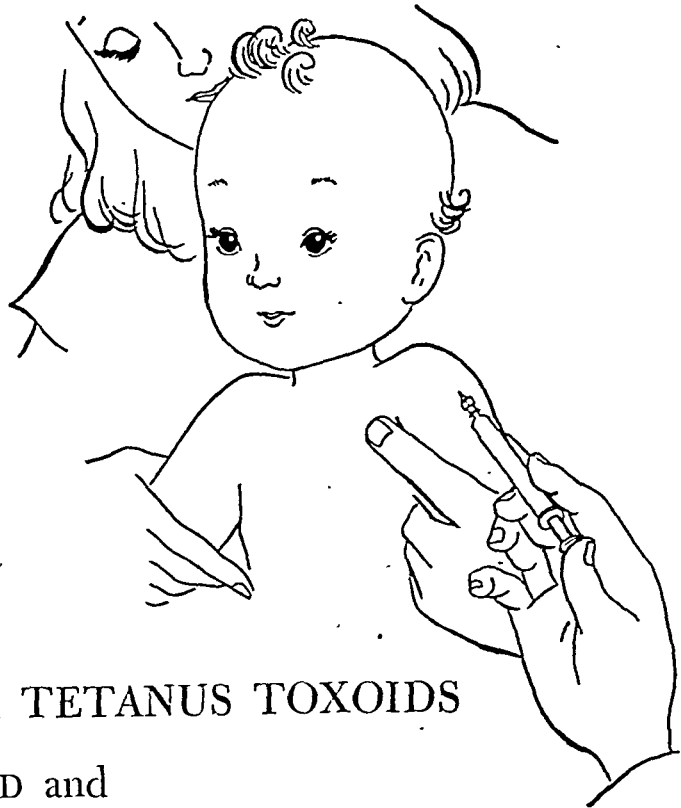


EXPECTANT MOTHER

THE LAYETTE'S ALL DONE, HOSPITAL RESERVATIONS ARE ALL ARRANGED--AND NOW YOUNG MRS. DOUGLAS IS BEGINNING TO WORRY ABOUT THE CARE AND FEEDING OF INFANTS !

FIRST-TIME PARENTS ARE ALWAYS PLEASED TO LEARN THAT THEIR OWN FIRST SOLID FOOD, GOOD OLD "CREAM OF WHEAT" IS STILL THE NUMBER-ONE CHOICE OF MANY DOCTORS FOR 1948'S NEW CROP OF BABIES. SMOOTH, ENRICHED 5 MINUTE "CREAM OF WHEAT" SUPPLIES ABUNDANT IRON AND FOOD-ENERGY, PROVIDES EXTRA CALCIUM, PHOSPHORUS AND VITAMIN B₁. COOKS TO COMPLETE DIGESTIBILITY FOR BABY IN ONLY 5 MINUTES OF BOILING. NO WONDER DOCTORS APPROVE !

"Cream of Wheat" and Chef are Registered Trade Marks and Reg. U. S. Pat. Off.



*for simultaneous
active immunization*

DIPHTHERIA and TETANUS TOXOIDS ALUM PRECIPITATED and PERTUSSIS VACCINE COMBINED

SQUIBB

Among the many advantages of simultaneous immunization against diphtheria, tetanus and pertussis are:

- *Injections fewer and of smaller total volume*
- *Local and systemic reactions reduced to a minimum*
- *Greater convenience for physician and patient*
- *Less discomfort for the patient*

DIPHTHERIA and TETANUS TOXOIDS Alum Precipitated and PERTUSSIS VACCINE COMBINED SQUIBB is given in three injections of 0.5 cc. each at monthly intervals. This amount provides a full immunizing dose of both Diphtheria and Tetanus Toxoids and 45,000 million killed H. pertussis organisms.

In 1.5 cc. vials, providing 1 complete immunization.

In 7.5 cc. vials, providing 5 complete immunizations.

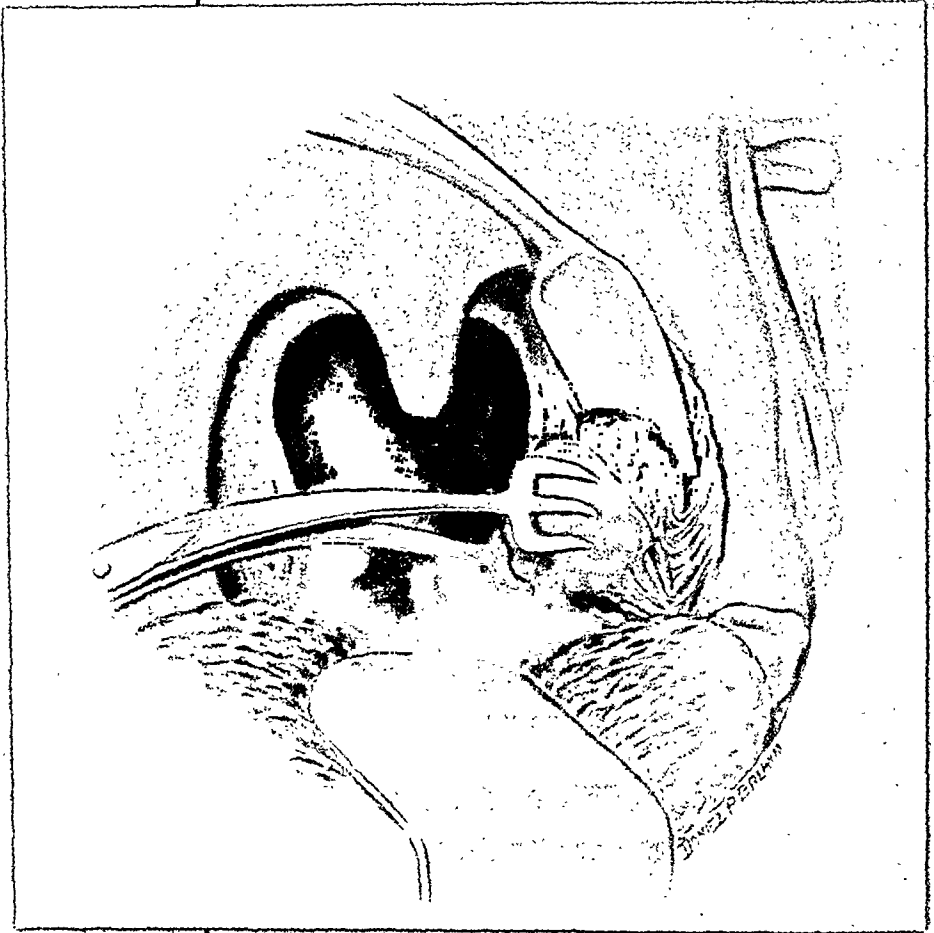
SQUIBB

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

May, 1948

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... for the



White

LABORATORIES, INC.,

Pharmaceutical Manufacturers, Newark 7, N. J.

Post-Tonsillectomy Throat

through "SALIVARY ANALGESIA"

In post-tonsillectomy care—and for relief of "sore throat" in acute and chronic tonsillitis and pharyngitis—salivary analgesia is provided by Aspergum; the analgesic is *continually* and *gradually* released as the preparation is chewed.

Aspergum brings pain-relieving acetylsalicylic acid into intimate and prolonged contact with crypts and folds of the mucosa seldom reached, even intermittently, by gargling or irrigation.

Gentle stimulation of muscular action helps relieve local spasticity and stiffness, at the same time hastening absorption of inflammatory products.

The pleasant flavor and form of Aspergum make it an easy means of providing analgesia and antipyresis, particularly for children.

Dillard's Aspergum contains $3\frac{1}{2}$ grains of acetylsalicylic acid in a palatable chewing gum base.

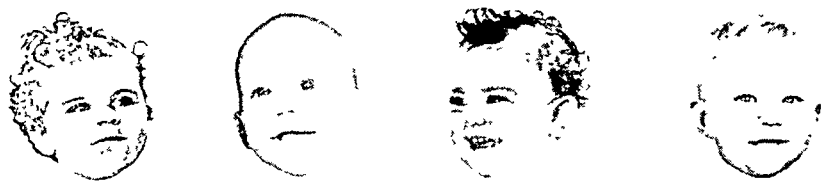
Dillard's

ETHICALLY
PROMOTED

A **Aspergum**
SALIVARY ANALGESIA-PLUS



More Babies are fed on



Carnation than any other



brand of evaporated milk!*

Here's why: Doctor, take a bow!
For the mothers who use Carnation give you as the reason, according to recent nation-wide surveys.

Nearly seventy-five percent of them (74.5%) state that Carnation was recommended by their doctor. And nearly five percent more (4.5%) report that it was

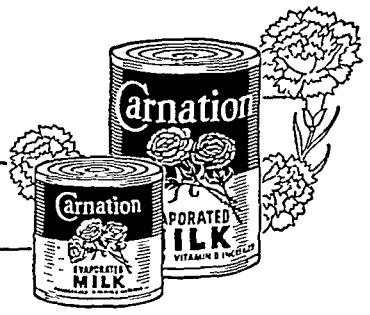
recommended by hospital or clinic.

And no one knows better than you why Carnation has such a wide acceptance in the medical profession. For your own experience confirms what laboratory tests prove: Carnation is one evaporated milk whose *quality* and *uniformity* you can depend upon—day in and year out.



**Nation wide surveys indicate that Carnation Milk is more widely used in infant feeding than any other brand of evaporated milk*

The Milk Every Doctor Knows
"From Contented Cows"

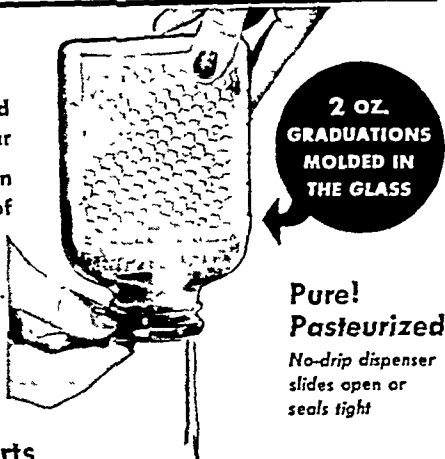


Growing number of Pediatricians report that

PURE HONEY Improves Weight Gains

and has These Other Apparent Advantages

- ... No tendency to be laxative
- ... Quickly absorbed, yet does not flood the blood stream with exogenous sugar
- ... Maintains blood sugar longer than sugars which contain higher levels of dextrose
- ... Increases the retention of calcium
- ... Indications of antihemorrhagic vitamin effect



Excerpts from Clinical Investigators' Reports

"Honey may have a distinct advantage in infant feeding over those carbohydrates which have a tendency to be laxative."*

"There is a tendency for slightly greater weight gains to occur with those infants receiving honey instead of some other forms of carbohydrates now commonly used."*

"It will be noted that for all the paired periods studied, the average retention of calcium was always higher if honey had been included in the formula."**

"In laboratory tests honey was proved to have a definite antihemorrhagic activity when incorporated in a basal ration to Vitamin K depleted subjects."***



Lake Shore Honey was used for these tests because it is pure, pasteurized, of guaranteed full strength and uniformity. It is produced under controlled conditions to regulate flavor and consistency.

We will gladly send you a small supply of Lake Shore Honey to use, so you may observe results in your own practice.

* "The Use of Honey as a Carbohydrate in Infant Feeding," by F. W. Schlutz, M.D., and Elizabeth M. Knott, Ph.D., *Journal of Pediatrics*, Vol. 13, No. 4, 465-473, October 1938

** "The Effect of Honey Upon Calcium," by E. M. Knott, Ph.D., C. F. Shukers, M.D., *Journal of Pediatrics* Vol. 19, N

*** "Antihemorrhagic Vitamin Effect of Honey," by A. E. Vivino, M. H. Haydak, L. S. Palmer and M. C. Tanquary, *Proceedings of the Society for Experimental Biology and Medicine*, 1943, 53, 9-11.



W. F. STRAUB & COMPANY
5500 Northwest Highway, Chicago 30, Ill.

Please send me a small supply of LAKE SHORE HONEY for use in my practice.

(Please write your name and address in the margin.)



The New Oral Method of Penicillin Administration to Infants and Children



Soluble Tablets Crystalline Penicillin provide a new and convenient means of instituting penicillin therapy in infants and young children. These small tablets of crystalline penicillin G potassium are composed entirely of penicillin, and contain neither binder nor excipient. Readily soluble, they may be administered with the milk formula to infants, or dissolved in milk or water before being given to young children. Thus the need for hypodermic injection is obviated in the treatment of many penicillin-responsive infections and administration can be made by the mother. Their presence in solution produces no discernible alteration in taste. Dosage, 100,000 units or more every 3 to 4 hours.

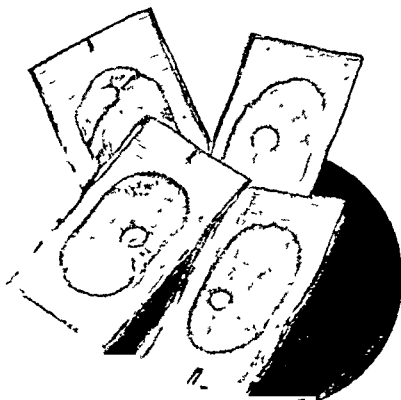
Each Soluble Tablet Crystalline Penicillin contains 50,000 units and is individually sealed in aluminum foil.

Supplied in boxes of 24 tablets and available at all pharmacies.

C.S.C. Pharmaceuticals

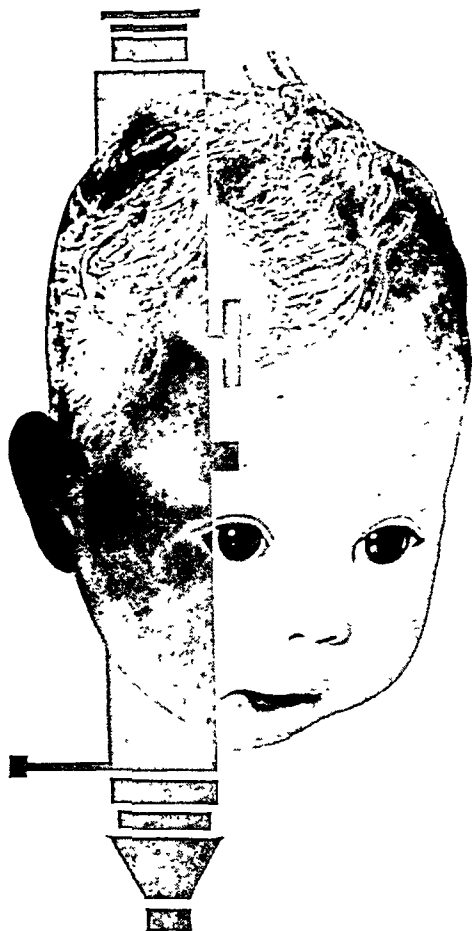
A DIVISION OF COMMERCIAL SOLVENTS CORPORATION
17 E. 42nd ST., NEW YORK 17, N. Y.

Soluble Tablets
Crystalline Penicillin



antiseptic baby oil used by 3400 hospitals

inhibits growth of common skin pyogens on newborn babies



bacteriostatic qualities proved. Independent research* has shown that Mennen

Antiseptic Baby Oil has an inhibiting effect on colonies of *Staphylococcus albus*, *Streptococcus* and *B. coli* (but not on spore forming organisms), found on the skin of newborn infants. For this reason Mennen Antiseptic Baby Oil is especially indicated for babies who manifest a tendency to common bacterial infections of the skin, or to eruptions either bacterial in origin or susceptible to aggravation by surface bacteria.

Clinical results support this research.

In 3 major hospitals, after the introduction of the Mennen Antiseptic Baby Oil technique, incidence of infant impetigo dropped from 7.8% to 0.47%.

A proven aid in curbing common infant skin irritations, Mennen Antiseptic Baby Oil is used by over 3400 hospitals, the majority of hospitals important in maternity work.

*Potter, Raymond T. and Abel, Arthur R., "A Study of Surface Bacteria of the Newborn and the Comparative Value of Cleansing Agents," *American Journal of Obstetrics and Gynecology* 31, No. 6, 1936.

Findings of the Moore Clinical Laboratory on Antiseptic Properties of Various Oils for the Skin of Babies.

mennen antiseptic baby oil

GELATINE IN THE DIET for DIABETES

— PEPTIC ULCER — COLITIS and

DIGESTIVE

DISORDERS



The unique qualities of Knox plain gelatine make it especially useful in certain diets. Knox gelatine is all protein, no sugar—unlike factory-flavored, acidified gelatine powders, which are about $\frac{7}{8}$ sugar and only about $\frac{1}{8}$ gelatine.

Knox plain, unflavored gelatine contains 9 of the 10 “essential”, and a majority of the 23 accepted amino acids that make up the proteins. It supplements the proteins of many food materials with which it can be combined to make attractive, highly appetizing and easily digested dishes.

Special Dietary Literature

At your request we shall be glad to mail any or all of the following booklets:—

- ...“Feeding the Sick and Convalescent”
- ...“Peptic Ulcer Dietary”
- ...“The Diet in Collitis and Digestive Disorders”
- ...“Feeding Diabetic Patients”
- ...“Reducing Diets and Recipes”

Address Knox Gelatine, Dept. O-3, Johnstown, N. Y.

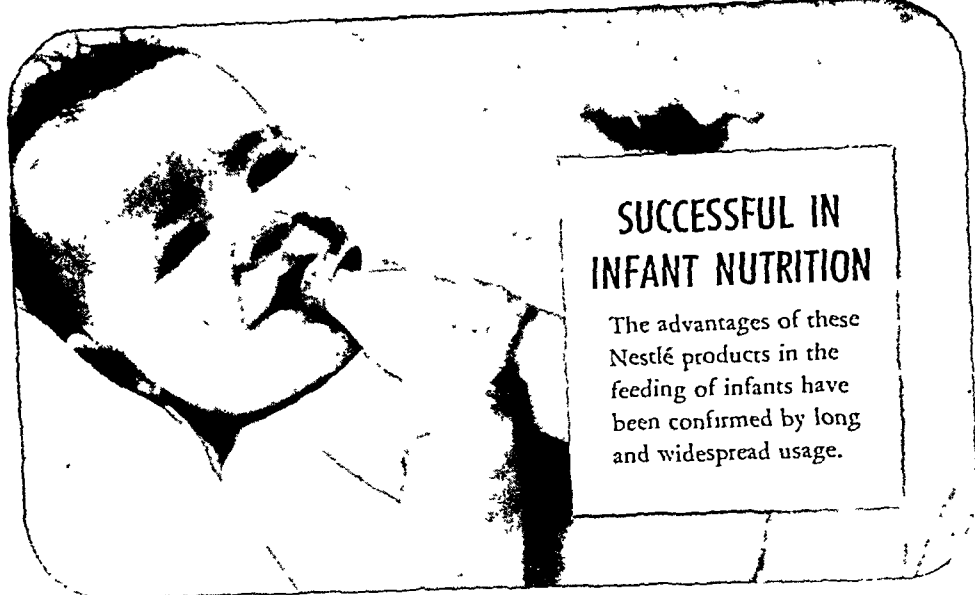


Two sizes—1 ounce (4 envelopes)
and $\frac{1}{2}$ pound (32 envelopes)

KNOX Gelatine

U. S. P.

All Protein—No Sugar



SUCCESSFUL IN INFANT NUTRITION

The advantages of these
Nestlé products in the
feeding of infants have
been confirmed by long
and widespread usage.



SPRAY DRIED

LACTOGEN

HOMOGENIZED
WHOLE COW'S MILK

Modified with
**MILK FAT
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Reinforced with **IRON**



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No advertising or feeding directions except to physicians

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Check the coupon below for literature and samples desired.

JP-5-48

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To meet the needs of pediatric patients in whom a complete vitamin supplement is indicated, White Laboratories announces a new, palatable, aqueous drop-dosage formula—

White's **MULTI-VI LIQUID**

Easily administered, water miscible and readily absorbed, non-alcoholic, this palatable new vitamin supplement is particularly adapted to prevention or correction of multiple vitamin deficiencies in infants and children.

FORMULA Each 0.6 cc. contains:

Vitamin A.....	5000 U.S.P. units
Vitamin D ₃	1000 U.S.P. units
Thiamine Hydrochloride.....	1.0 milligrams
Riboflavin.....	0.4 milligrams
Pyridoxine Hydrochloride.....	1.0 milligrams
Sodium Pantothenate.....	2.0 milligrams
Nicotinamide.....	10.0 milligrams
Ascorbic Acid.....	50.0 milligrams

NOTE: Vitamin D is present as Vitamin D₃, which, unlike viosterol, is chemically identical with the "D" of cod liver oil. Vitamin C is present in optimal amount—meets the needs of those who cannot tolerate natural food sources of this vitamin.

RECOMMENDED DOSAGE:

For young infants: 0.3 cc. daily.

For older infants and children: 0.6 cc. daily.

May be given in the formula or directly. Accurate dosage assured by accompanying calibrated dropper.

ECONOMICAL: Cost of protective daily dosage for average infant—only 2 cents!

essential vitamins for infants in a stable liquid form

... and for Selectivity in Pediatric Practice

WHITE'S "INTEGRATED" VITAMIN FORMULAS

To satisfy the varying vitamin requirements of infancy and childhood, White Laboratories now offer the physician a well-rounded group of related formulas thereby providing the clinical advantage of greater flexibility.

The products may be used singly or in combination depending on individual needs. In addition to Multi-Vi Liquid, they include:

WHITE'S COD LIVER OIL CONCENTRATE, N.H.R.

Liquid • Tablets • Capsules

—the natural vitamins A and D of time-proved cod liver oil in three palatable, stable, convenient dosage forms—well suited for rickets' prophylaxis and treatment from 14 days to 14 years.

ETHICALLY

WHITE'S MULTI-BETA LIQUID

—the nutritionally important *vitamin B factors* in a water-miscible vehicle—presented in proportion to their inadequacy in average diets of early infancy.

PROMOTED

ulti-vi Liquid

Pharmaceutical Manufacturers, Newark 7, N. J.

Recent Advances In Combating Morning Sickness

Morning sickness or the tendency to early morning nausea and vomiting is presumptive of pregnancy in the healthy woman who missed a menstrual period. The symptom occurs earlier, more constantly and severely in primiparas than in multiparas and more in nervous high-strung temperaments than in placid women. Continuance of this symptom renders probable the life of the fetus because the vomiting ceases when the child dies. The feeling passes once the woman feels fetal activity.

Nausea and vomiting of early pregnancy is a biochemical phenomenon accompanied by quick fatigue, weakness and fainting spells. If severe, there is no acidosis because the blood pH is normal and the carbon dioxide high or low. The vomiting causes increased blood concentration, decreased serum protein, loss of electrolyte and hypoglycemia. The urine shows acetone and diacetic acid, indicating a ketosis.

During the first trimester a high carbo-

hydrate diet with KARO* Syrup is preferred by most women to prevent vomiting. Frequent small carbohydrate meals of skimmed milk, KARO, toast, rice, potato, dates, and figs are most effective.

The nutritional problem of pregnancy is always the same. Today the high carbohydrate requirement during the first months of pregnancy is fulfilled by KARO as adequately as a generation ago.

KARO is a balanced mixture of low sugars; well tolerated, palative, hypoallergic, resistant to fermentation, easily digested, readily absorbed, and non-laxative. Most of the articles of diet given below can be reinforced with KARO to enrich the carbohydrate content.

MEDICAL DIVISION
CORN PRODUCTS REFINING CO.
17 Battery Place, New York 4, N. Y.

*KARO is a registered trade-mark distinguishing this product of the Corn Products Refining Co., New York, N.Y.



HIGH CALORIC, HIGH CARBOHYDRATE, LOW FAT DIET

(During the first trimester)

Breakfast

FRUIT—Orange or grapefruit juice with KARO or sugar. Baked apple, applesauce, banana or stewed prunes with KARO or sugar.

CEREAL—Corn meal, corn flakes, hominy, oatmeal, rice flakes with KARO or sugar and skim milk. Waffles with KARO.

BREAD—Cracked, whole wheat or white bread, toasted, with KARO, jam, jelly or marmalade.

BEVERAGES—Coffee, tea, skim milk, cocoa or postum with KARO or sugar.

Between Meals

Skim milk, sherbet, lemonade, tea with KARO and zwieback, crackers or toast. Vitamin and mineral supplements

Lunch and Dinner

JUICE OR SOUP—Fruit or vegetable juice Consomme, bouillon, vegetable soup or broth with rice, barley, macaroni or noodles, asparagus.

VEGETABLE—Artichoke, asparagus, beets, carrots, peas, potato, succotash, tomato or turnip as salad with pot cheese.

FRUIT—Apples, apricots, bananas, figs, canned fruits, pears, peaches or prunes.

BREAD—As for breakfast.

DESSERT—Stewed or canned fruit; corn starch, rice or tapioca pudding; Irish or lemon blanc mange, cake, gelatin, junket; sherbet and skim milk.

BEVERAGE—Coffee, tea, skim milk, lemonade, ginger ale.

In This New "Self Selected" Diet Regimen..



IN THE modern day infant feeding plan, where the infant is permitted to choose what he likes from a group of foods offered, Libby's Baby Foods prove especially advantageous. Through Libby's exclusive process of homogenization cellulose cell capsules are ruptured and all fibrous material is reduced to microscopic particles. Hence Libby's Baby Foods are satin-smooth in texture, the nutrients are dispersed homogeneously throughout the food mass, and there is no "separating out" of the solids from the liquid. Libby's frequently have been fed as early as the sixth week of life, conditioning the infant to a wide variety of foods.

Beets • Carrots • Green Beans • Peas • Spinach • Squash • Vegetable Soup • Mixed Vegetables • Garden Vegetables • Liver Soup • Vegetables with Bacon • Vegetables with Beef and Barley • Vegetables with Lamb • Apples and Apricots • Apples and Prunes • Apple Sauce • Apricot-Farina • Peaches • Peaches-Pears-Apricots • Pears and Pineapple • Prunes (with Pineapple Juice and Lemon Juice) • Custard Pudding

Libby, McNeill & Libby • Chicago 9, Illinois



Sweetose*

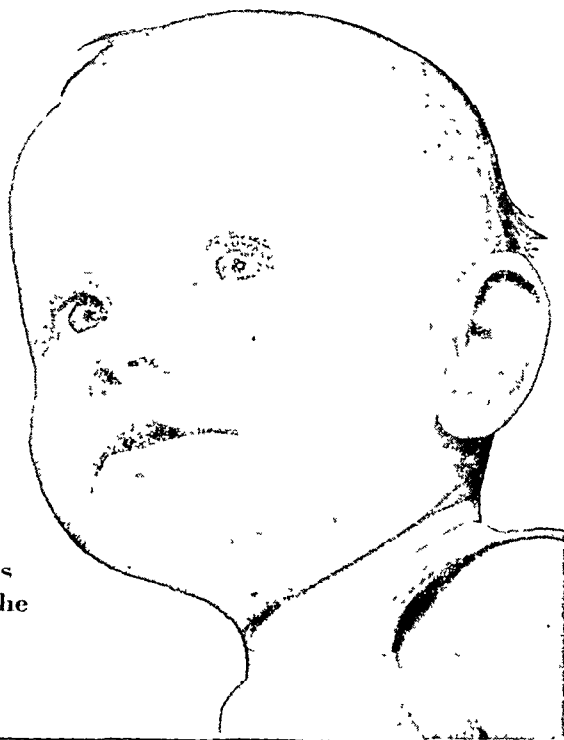
Ideal carbohydrate supplement for infant feeding formulas

Quickly soluble

Readily digestible

Extra rich in dextrose and maltose, Sweetose offers unusual nutritional advantages in infant feeding formulas. Sweetose provides substantially higher amounts of both dextrose and maltose, in contrast to ordinary corn syrups. The possibility of gastrointestinal irritation is greatly minimized by the use of Sweetose.

Write for further details



*"Sweetose" is a trade-mark of the A. E. Staley Mfg. Co., Decatur, Illinois, registered in the U. S. Pat. Off.

A. E. Staley Mfg. Co.

Box 1091, DECATUR, ILLINOIS



Representative Analysis of Sweetose White Syrup	Representative Analysis of Ordinary Corn Syrup
---	--

Moisture.....	25.2.....	26.6
Dextrose.....	25.6.....	14.7
Maltose.....	23.4.....	13.9
Higher Sugars..	11.0.....	13.6
Dextrines.....	8.3.....	24.8
Sucrose.....	6.3.....	6.2
Ash.....	0.2.....	0.2
Available Carbohydrates..	74.6.....	73.2
Calories per fluid oz.....	120.0.....	118.5

No added flavoring or salt.

In allergic disorders...

When symptomatic relief through use of an antihistaminic drug is desired, reference will be given to histamine antagonists that possess these two characteristics:

1. **Efficacy**—to relieve bothersome symptoms.
2. **Low Toxicity**—to make these benefits available to the greatest possible number of patients.

Neo-Antergan Maleate*, the new Merck antihistaminic, possesses these desired characteristics to a clinically significant degree.

In addition to findings from extensive experimental work, there now are on hand clinical reports of more than 1,000 cases of allergy treated with Neo-Antergan. Results attest to effective symptomatic relief in many cases of Hay Fever, Pruritus, Urticaria, Vasomotor Rhinitis, Atopic Dermatitis, Allergic Drug Reactions, and certain other allergic disorders. Side reactions were absent in the large majority of patients. When they occurred, they were generally mild and transient. Discontinuance of treatment because of the severity of side effects was necessary in only about one and one-half per cent of patients.

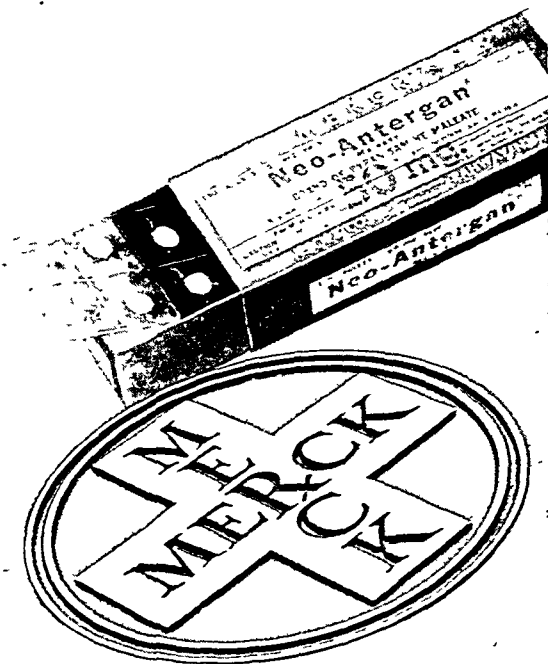
Your local pharmacy stocks Neo-Antergan Maleate in 25 mg. and 50 mg. tablets, supplied in boxes of 100.

NEO-ANTERGAN®

MALEATE

(Brand of Pyranisamine Maleate)

(N-*p*-methoxybenzyl-N', N'-dimethyl-N-*a*-pyridylethylene-diamine maleate)



MERCK & CO., Inc. RAHWAY, N.J.

Manufacturing Chemists

*Neo-Antergan is the registered trade-mark of Merck & Co., Inc. for its brand of Pyranisamine



● Custom-made clots are now available with Gelfoam.*

● The old surgeon may have dreamed of the day when a ready-made clot would staunch oozing surfaces, capillary bleeding, trickling from small veins, hemorrhage from resected tissues.

The surgeon of today has at hand a custom-made clot with GELFOAM, the absorbable hemostatic gelatin sponge. Cut or molded to the exact specifications of any wound, and applied with or without thrombin, GELFOAM may be left in situ without fear of tissue reaction.

**Trademark, Reg. U. S. Pat. Off.*

Gelfoam

Upjohn
KALAMAZOO 99 MICHIGAN

fine pharmaceuticals since 1886

facts about Formulac



What is FORMULAC Infant Food? It is a concentrated milk containing *all the vitamins and minerals* a normal, growing baby is known to need. Incorporating the vitamins *into the milk itself* lessens the risk of error in supplementary administration.

FORMULAC contains vitamins of the B complex, Vitamin C in stabilized form, Vitamin D (800 U.S.P. units), copper, manganese, and easily assimilated ferric lactate. No carbohydrate has been added.

FORMULAC is in convenient liquid form, for easy preparation. The addition of carbohydrate—in the type and amount the individual child needs—creates a complete infant diet. FORMULAC is used successfully both in normal and in difficult feeding cases.

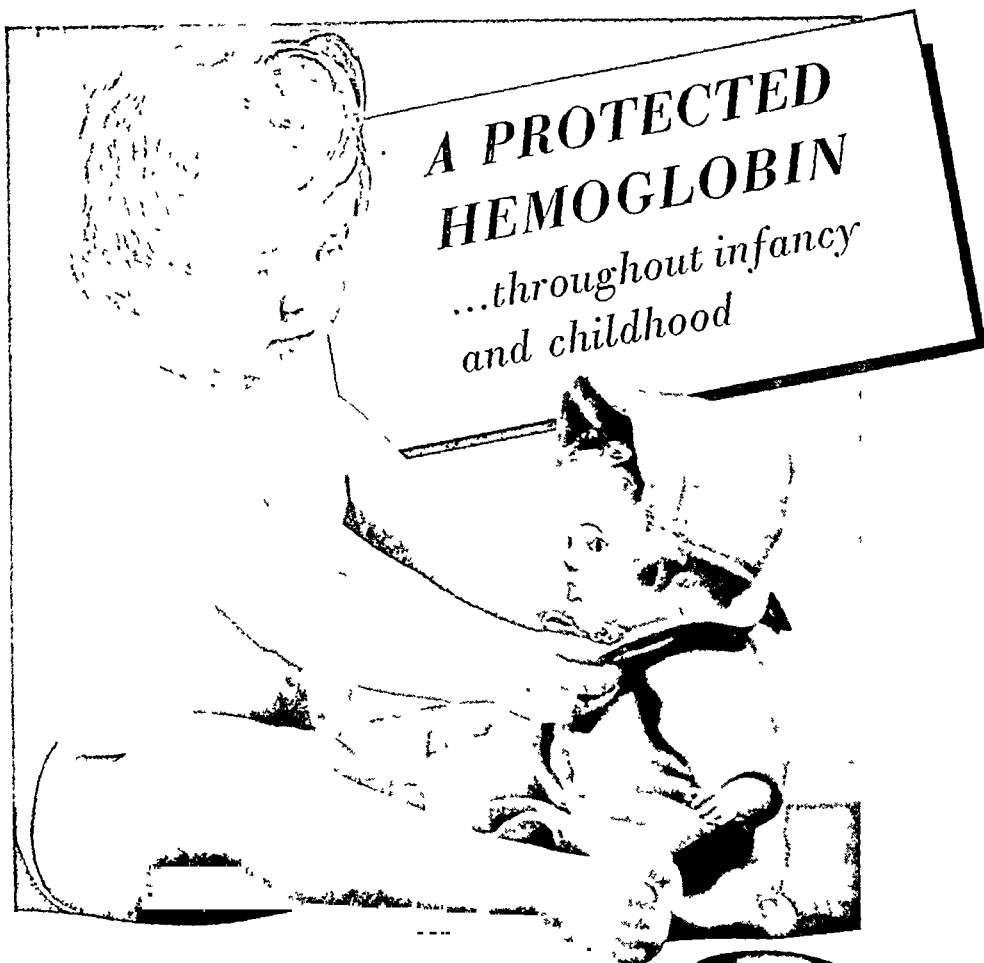
FORMULAC has been clinically tested and proved. It is promoted ethically. A product of National Dairy Research, it is available at grocery and drug stores everywhere, priced within range of even low budgets.

DISTRIBUTED BY KRAFT FOODS COMPANY

NATIONAL DAIRY PRODUCTS COMPANY, INC.
NEW YORK, N. Y.

• For further information about FORMULAC, drop a card to National Dairy Products Company, Inc., 230 Park Avenue, New York 17, N. Y.





During the early years of life the expanding blood volume makes heavy demands upon iron stores to satisfy hemoglobin requirements.

Copperin "B" promptly replenishes these inroads upon iron reserves — protecting the hemoglobin levels. Due to the presence of the catalyzing copper sulphate *all* of the iron ammonium citrate is available for use. Hence, the iron is present in very small quantity—32 Mg. per capsule. Copperin is well tolerated, causes no stomach irritation and being water soluble, may be taken in fruit juices, milk or feeding formula.

Write for samples and pediatrician's literature

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Mount Vernon, New York



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Saved
by a Smile
...Again!

Think how many more frantic calls for help you'd be saved, if more babies took their first solid food after milk (usually cereal) with a smile! There seems to be less trouble for everybody (doctors, babies and mothers) when tots get started on *finely strained, good-tasting* Gerber's Cereals.

More smiles per spoonful! That's the happier feeding pattern reported by thousands of mothers when Gerber's Cereals and babies get together—right from the start. And, the pattern maintains straight through babyhood if . . .

Baby is pleasantly surprised with a rotating schedule of Gerber's good-tasting Cereal Food, Strained Oatmeal and Barley Cereal. Gerber's ready-to-serve Cereals, so easily digested, are a significant secondary source of *protein*. Fortified with much-needed iron, *plus calcium and yeast*. So baby gets *better-than-whole-grain* values of minerals and B-complex vitamins from Gerber's!

Babies
are our
business...
our only
business!



Gerber's
BABY FOODS
Fremont, Mich.—Oakland, Cal.

For FREE SAMPLES of Gerber's 3 Cereals—
plus professional reference cards, write
to Gerber's, Dept. 277-8 Fremont, Mich.



3 CEREALS

20 STRAINED FOODS

15 JUNIOR FOODS

the preferred

PERTUSSIS IMMUNE SERUM—*human* IN VACUUM-DRIED FORM



This serum—established as the agent of choice in the treatment of, and passive immunization against, whooping cough—is now available to physicians everywhere.

Vacuum dehydration by the 'LYOPHILE' process provides high stability (a 5-year dating) and permits optimal concentration.

Standard price: \$6.50 per dose,

i.e., vial containing 20 cc. of serum, vacuum-dried.

3 to 4 doses generally required in treatment.

24-hour service to handle telegraphic orders.

For literature and full information, write to:

The PHILADELPHIA
SERUM

EXCHANGE *A Non-profit Organization*

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
1740 Bainbridge Street, Philadelphia 46, Pennsylvania



30 day wonder.

The new-born infant is truly a "30-day wonder" taking in his stride the sudden changes birth imposes and adjusting accordingly. The rapid increase in weight is, alone, a feat no adult could duplicate. The right start on the right feeding is of vital importance—particularly during the first 30 days when infant mortality is at its highest and when he not only must regain his birthweight *but keep on gaining* if he is to survive.

'Dexin' has proved an excellent "first carbohydrate" because of its high dextrin content. It (1) resists fermentation by the usual intestinal organisms, (2) tends to hold gas formation, distention and diarrhea to a minimum, and (3) promotes the formation of soft, flocculent, easily digested curds.

Simply prepared in hot or cold milk, 'Dexin' brand High Dextrin Carbohydrate provides well-taken and well-retained nourishment. 'Dexin' *does* make a difference.

Literature on request

HIGH DEXTRIN CARBOHYDRATE

'Dexin'

BRAND

Composition—Dextrins 75% • Maltose 24% • Mineral Ash 0.25% • Moisture 0.75% • Available carbohydrate 99% • 115 calories per ounce • 6 level packed tablespoonfuls equal 1 ounce • Containers of twelve ounces and three pounds • Accepted by the Council on Foods and Nutrition, American Medical Association.
'Dexin' Reg. Trademark



BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9 & 11 East 41st St., New York 17, N. Y.

May, 1948

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Why

One Fourth to One Third?

In the minds of most persons, the size of both luncheon and dinner is fairly well established. Yet the breakfast these very same individuals eat is subject to great variation—from a large meal when a leisurely breakfast can be enjoyed to a totally inadequate meal when time is short. Not only adults, but many teen-age children, are guilty of this practice of eating a poor breakfast or skipping breakfast entirely.

Nutrition authorities are agreed that breakfast should provide from one-fourth to one-third of the day's caloric and nutrient needs. If less is eaten, morning hunger and inefficiency develop. Furthermore the other two meals of the day can hardly supply the nutrients and calories the deficient breakfast failed to provide.

To encourage better breakfast eating habits, a basic breakfast pattern consisting of fruit, cereal, milk, bread and butter has been widely endorsed. It provides a nutritionally adequate morning meal, is notably economical, and is universally available. The cereal serving—hot or ready-to-eat breakfast cereal, milk, and sugar—is an important main dish of this meal, adding taste appeal, many nutritional essentials, and almost endless variety.

The table indicates the nutrient values of this basic breakfast and the contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk and 1 teaspoonful of sugar.



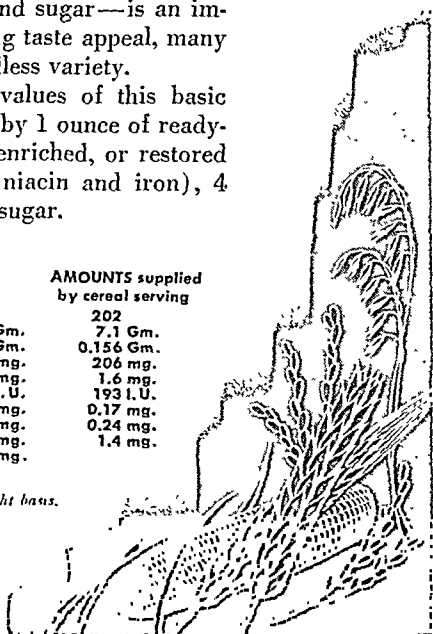
The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

BASIC BREAKFAST	TOTALS supplied by Basic Breakfast	AMOUNTS supplied by cereal serving
Orange juice, 4 oz.;		
Ready-to-eat or		
Hot Cereal, 1 oz.;	CALORIES..... 611	202
Whole Milk, 4 oz.;	PROTEIN..... 20.7 Gm.	7.1 Gm.
Sugar, 1 teaspoon;	CALCIUM..... 0.465 Gm.	0.156 Gm.
Toast (enriched,	PHOSPHORUS 488 mg.	206 mg.
white), 2 slices;	IRON..... 3 mg.	1.6 mg.
Butter, 5 Gm.	VITAMIN A..... 1074 I. U.	193 I. U.
(about 1 teaspoon);	THIAMINE..... 0.52 mg.	0.17 mg.
Whole Milk, 8 oz.	RIBOFLAVIN..... 0.87 mg.	0.24 mg.
	NIACIN..... 2.3 mg.	1.4 mg.
	ASCORBIC ACID . . 64.8 mg.	

* Composite average of all breakfast cereals on dry weight basis.

CEREAL INSTITUTE, INC.

A research and educational endeavor devoted to the betterment of national nutrition.
135 South La Salle Street • Chicago 3



Q: What food can solve one of your warm-weather feeding problems?

A: ***Instant Ralston.** It cooks in 10 seconds, so mothers find it easy to prepare—assuring your young patients a hot, nourishing cereal during summer months.*

Instant Ralston is whole wheat with added wheat germ. Provides energy for increased summer activities. Gives the advantages of hot cereal as an aid to digestion—sense of well-being.

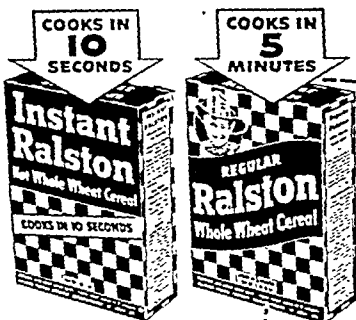
Supplies extra thiamine, extra protein . . . because it's $2\frac{1}{2}$ times as rich in wheat germ as whole wheat. And wheat germ is one of the best food sources of thiamine, which helps boost lagging summer appetites. Wheat germ provides, too, protein of biological value comparable to meat, milk and cheese proteins.

Good reasons for suggesting Instant Ralston this summer

Free

Feeding Direction Forms for four age groups: birth to 3 months; 3 to 6 months; 6 to 10 months; over 10 months.

Easy to use. Adaptable. Available in pads of 50 each, imprinted with your name and address if you wish.



USE THIS COUPON!

Ralston Purina Company, Nutrition Service
JP-8 Checkerboard Square, St. Louis 2, Mo.
Please send, no cost or obligation, samples of
Feeding Direction Forms, C848, so I may
order pads as needed.

Name _____ M.D.

Address _____

City _____ Zone _____ State _____

S-M-A[®] builds husky babies

Fat is the hinge of the S-M-A formula. The specially reconstituted fat in S-M-A is almost identical with the fat in human milk, and is present in the same proportion. The only carbohydrate used in S-M-A is Lactose, the physiologic carbohydrate, fed in physiologic amount (7%) as in human milk. Because of the unsaturated fatty acids in its formula, S-M-A supplies the "ounce of prevention" against eczema. S-M-A closely approximates mother's milk.

The S-M-A formula is well suited to modification, as the physician may wish, for special feeding problems.



*How much punishment
can a handful of baby take?*



**—with HYPERTUSSIS-CUTTER
your dosage is "tailored to size"**

Hyperimmune serum has long been recognized as specific in the treatment of pertussis. But because the most serious cases involve very small infants, Hypertussis-Cutter offers two distinct advantages:

1. Its antibody content is concentrated — dosage is small.
2. The source is hyperimmunized adult human blood.

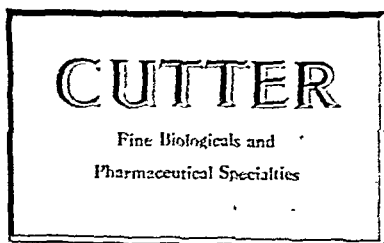
Hypertussis is a water-clear, homologous globulin, obtained from fractionating pooled plasma of hyperimmunized adult human donors. 2.5 cc. Hypertussis is actually the equivalent of 25 cc. hyperimmune serum, or 50 cc. hyperimmunized whole blood—providing consistent globulin concentration.

Thus, while providing adequate antibodies, the small dosage volume prevents painful tissue distention and trauma. Moreover, the human blood source assures you that Hypertussis is reaction-free.

While Hypertussis (Anti-Pertussis Serum, Human) is the most rational therapeutic agent yet tried in treating whooping cough, it is also being used successfully in protection of known contacts and susceptibles.

When you want a bucketful of potency, in a thimble-size syringe, for a handful of baby—specify Hypertussis at your pharmacy.

CUTTER LABORATORIES • Berkeley 1, Calif.

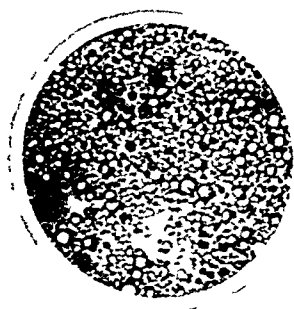


An IMPROVED TECHNIQUE for controlling HOT-WEATHER MILIARIA

INCIDENCE of miliaria among infants born in summer months (May through September) often runs as high as 50%, hospital records show.

But when new Johnson's Baby Lotion is used for routine skin care, cases of miliaria drop to a remarkable low!

For two years, Johnson's Baby Lotion was tested on many hundreds of newborns. Its performance in preventing miliaria (which may lead to more serious secondary infections) was outstanding—even in hot summer months.



Johnson's Baby Lotion leaves a discontinuous film. (1000 x)



Lotion leaves a discontinuous film

Johnson's Baby Lotion is a finely homogenized emulsion of mineral oil and lanolin in water, with a mild antiseptic (hydroxy quinoline) added. As the water phase evaporates, a dis-

continuous film (see photomicrograph) is left on the infant's skin.

This permits normal heat radiation, and allows perspiration to escape readily—thus lessening the danger of irritation.



JOHNSON'S BABY LOTION

Johnson & Johnson

FREE! Mail coupon for 12 distribution samples!

Johnson & Johnson, Baby Products Division
Dept. A-3 New Brunswick, N. J.

Please send me, free of charge, 12 distribution samples of Johnson's Baby Lotion.

Name

Street

City State

Offer limited to medical profession in U.S.A.

THE JOURNAL OF PEDIATRICS

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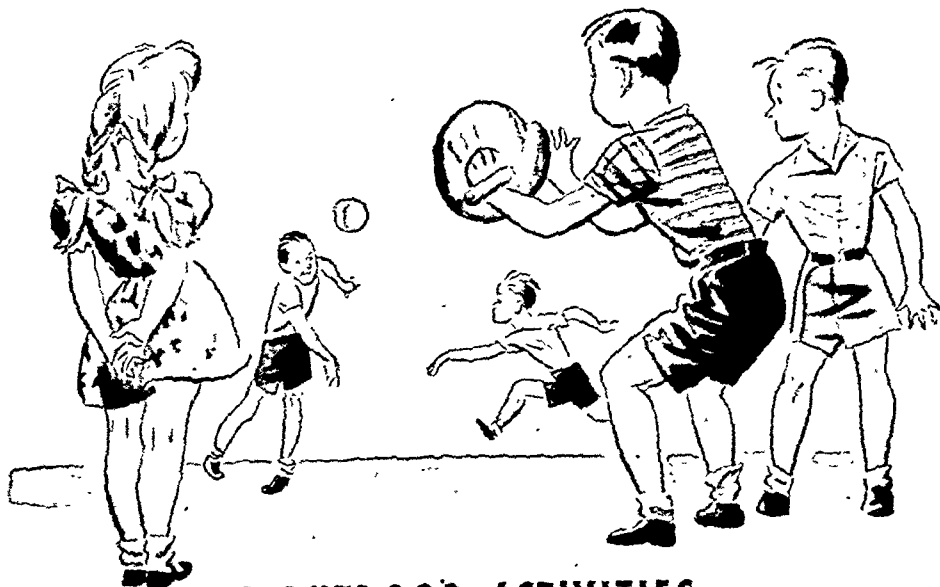
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AS OUTDOOR ACTIVITIES

Increase Nutrient Demands

The greater physical activity which all youngsters enjoy during the summer months creates increased caloric and nutrient demands to make possible the augmented energy expenditure. Not only must a larger amount of calories be provided, but also must the B complex vitamin intake be increased to make possible maximal utilization of carbohydrate. Unnecessary weight loss may occur if these nutritional demands are not satisfied.

An excellent means of providing

the greater quantities of nutrients needed is found in the delicious food drink made by mixing Ovaltine with milk. Children enjoy its delightful taste, and find chocolate flavored Ovaltine especially tempting. Served with between meal snacks or as a mealtime beverage, this dietary supplement is equally acceptable. The table of composition indicates the wealth of essential nutrients provided by Ovaltine made with milk. Note that virtually every essential nutrient is provided in significant quantity.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

Three servings daily of Ovaltine, each made of $\frac{1}{2}$ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES.....	559	VITAMIN A.....	3700 I.U.
PROTEIN.....	32.1 Gm.	VITAMIN B ₁	1.15 mg.
FAT.....	37.5 Gm.	PIRIBLAVIN.....	2.10 mg.
CARBOHYDRATE.....	64.8 Gm.	NIACIN.....	8.8 mg.
CALCIUM.....	1.12 Gm.	VITAMIN C.....	32.0 mg.
PHOSPHORUS.....	0.54 Gm.	VITAMIN D.....	411 I.U.
IRON.....	12.0 mg.	COPPER.....	0.50 mg.

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.



Baby Breck

O I N T M E N T

For Aiding Diaper Rash .

Baby Breck Ointment is a bland, soothing ointment for diaper rash and chafed areas of the skin. It may be applied at every diaper change or in the evening as a preventative measure. Baby Breck Ointment was formulated to minimize allergic reaction. It helps to protect the sensitive skin of a baby with a resistant coating.

JOHN H. BRECK, INC. MANUFACTURING CHEMISTS SPRINGFIELD 3 MASSACHUSETTS
CANADIAN ADDRESS 310 SLATER STREET . OTTAWA

WHEN SENSITIVITY TO COW'S MILK LACTALBUMIN IS SUSPECTED

Meyenberg Evaporated GOAT MILK

THE SUPERIOR-QUALITY
NATURAL MILK FOR
INFANTILE ECZEMA
AND DIFFICULT
FEEDING CASES



PRODUCTS

MEYENBERG Evaporated Goat Milk has gained outstanding national acceptance because it is *uniform, sterile and more palatable*. Prescribe or recommend Meyenberg whenever Cow's Milk allergy is suspected.



Available in 14-ounce hermetically-sealed containers
at all pharmacies

Advertised only to
the medical profession

Now
Available
in
Unlimited
Quantities

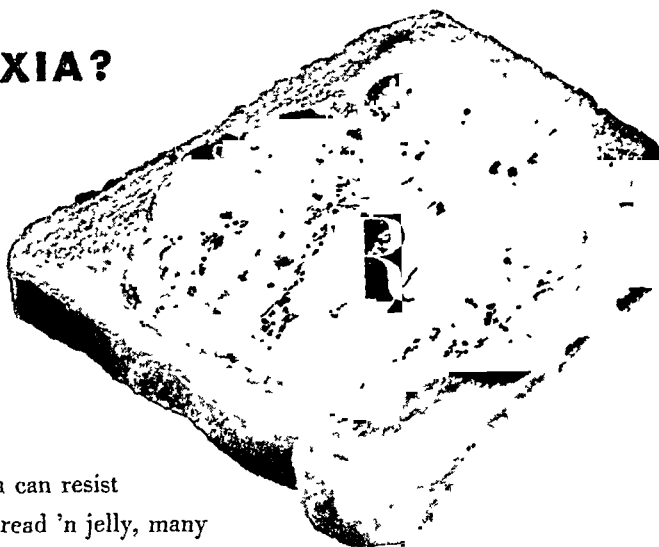
SPECIAL MILK PRODUCTS, INC.

11500 TENNESSEE AVENUE • LOS ANGELES 25, CALIFORNIA

EVER TRY

BREAD 'N JELLY THERAPY

IN ANOREXIA?



Because few children can resist a luscious piece of bread 'n jelly, many pediatricians are using it as a weapon to combat anorexia—the commonest complaint in pediatrics. With a spoonful of 'Ryzamin-B' No. 2 added to the spread, this universal favorite becomes a potent source of B complex vitamins to provide the needed stimulus to lagging appetites. So pleasant is its rich, honey-like flavor that children seldom are aware that they are taking medicine. Most children take 'Ryzamin-B' No. 2 right off the spoon; all children enjoy it when given as a delicious spread mixed with jam or peanut butter or dissolved in milk, fruit juice or their favorite beverage.

Containing the *natural* B complex as a concentrate of *Oryza sativa* (American rice) polishings, 'Ryzamin-B' No. 2 also supplies potent synthetic B factors.

'RYZAMIN-B'

BRAND RICE POLISHINGS CONCENTRATE **NO. 2**

WITH ADDED THIAMINE HYDROCHLORIDE, RIBOFLAVIN AND NICOTINAMIDE
TUBES OF 2 OZ. AND BOTTLES OF 8 OZ



'Ryzamin B' registered trademark



BURROUGHS WELLCOME & CO (U.S.A.) INC., 9 & 11 EAST 41ST STREET, NEW YORK 17

Why do
Irene and
Mary need
vitamin D
?

Growing children require vitamin D mainly to prevent rickets. They also need vitamin D, though to a lesser degree, to insure optimal development of muscles and other soft tissues containing considerable amounts of phosphorus . . .

Milk is the logical menstroom for administering vitamin D to growing children, as well as to infants, pregnant women and lactating mothers. This suggests the use of Drisdol in Propylene Glycol, which diffuses uniformly in milk, fruit juices and other fluids.

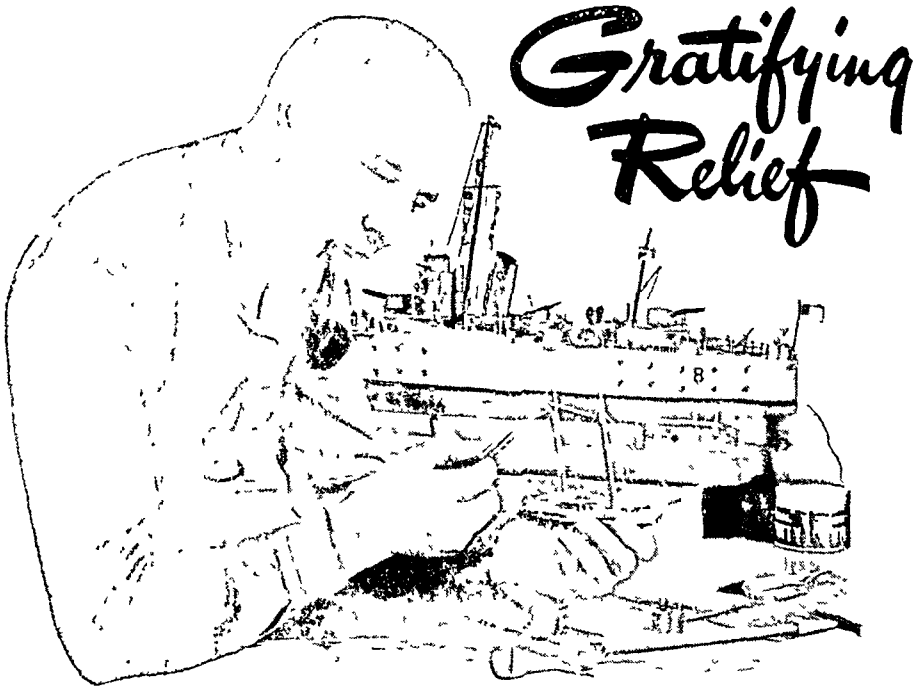
Average daily dose for infants 2 drops, for children and adults 4 to 6 drops, in milk. Available in bottles of 5, 10 and 50 cc with special dropper delivering 250 U.S.P. units per drop



DRISDOL IN PROPYLENE GLYCOL
MILK DIFFUSIBLE VITAMIN D PREPARATION
ODORLESS • TASTELESS • ECONOMICAL

DRISDOL, trademark Reg. U.S. Pat. Off.
& Canada Brand of Crystalline Vitamin D₂
(calciferol) from ergosterol

Winthrop-Stearns INC.
NEW YORK 13, N. Y. WINDSOR ONT.



**Gratifying
Relief**

Ambulant patients are promptly relieved of distressing urinary symptoms in a large percentage of cases through the simple procedure of administering Pyridium in a dosage of 2 tablets *t.i.d.*

Following oral administration, Pyridium produces a definite analgesic effect on the urogenital mucosa. This palliative action contributes to the prompt and effective relief that is so gratifying to patients suffering from disturbing symptoms such as painful, urgent, and frequent urination, nocturia, and tenesmus.

Therapeutic doses of Pyridium may be administered throughout the course of treatment of uncomplicated cystitis, pyelonephritis, prostatitis, and urethritis, with virtually no danger of serious side reactions.

*... through
Urogenital
Analgesia*

Literature on Request

PYRIDIUM®

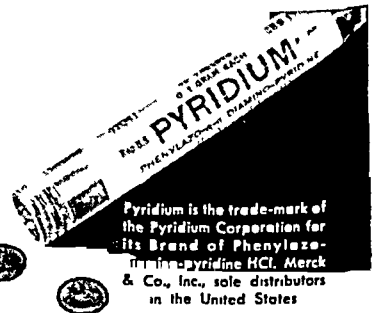
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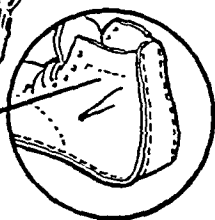
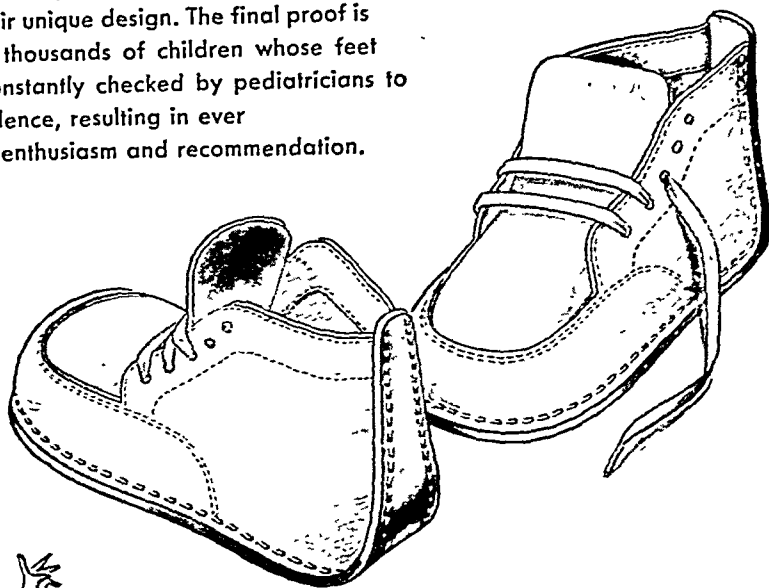


Why Pediatricians Recommend

JUMPING JACKS
SOFT SHADES FOR HARD WEAR

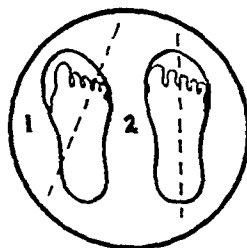
For Children 6 Months to 4 Years Old

The Superiority of Jumping Jack shoes for youngsters is evident in their unique design. The final proof is in the countless thousands of children whose feet have been constantly checked by pediatricians to justify their confidence, resulting in ever increasing enthusiasm and recommendation.



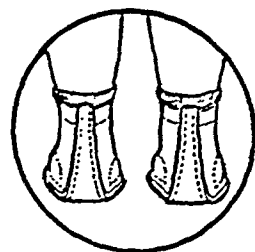
Exclusive Patented Extension Sole

No other shoe offers this innovation in construction—a single piece of leather from toe to top of shoe—with all seams on the outside—no striking edges that wear and influence walking habits.



Prevents Friction Retains Shape

Figure 1 (left) shows pressure resulting in cramped foot, friction due to conventional shoe. Figure 2 (right) allows foot freedom, equal distribution of weight and flexibility.



Builds Confidence For "First Steps"

Patented, Jumping Jack support helps prevent ankles from turning . . . assures correct, healthful walking from the start. And excellent materials and craftsmanship afford extra satisfaction.

VAISEY-BRISTOL SHOE COMPANY, INC.
625 SO. GOODMAN STREET • ROCHESTER 7, N. Y.

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By Wilson E. Huges, M.D., and Morton L. Hammond, M.D., Baltimore, Md.

CLINICAL SIGNS AND DEVELOPMENT OF SURVIVORS OF KERNICTERUS DUE TO RH SENSITIZATION

By Lottie Lande, M.D., Dixon, Ill.

CONSTITUTIONAL STatural OVERGROWTH AND INCREASED LOWER BODY SEGMENT WITH NORMAL SEXUAL DEVELOPMENT IN A FAMILY OF FOUR.

By George B. Dorff, M.D., Brooklyn, N. Y.

A REVIEW OF BOECK'S SARCOID WITH ANALYSIS OF TWELVE CASES OCCURRING IN CHILDREN.

By Ross B. Cone, M.D., Durham, N. C.

MACROCHEILIA FROM LABIAL GLAND HYPERPLASIA TREATED BY PLASTIC SURGERY.

By E. T. McEnery, M.D., and K. W. Penhale, D.D.S., M.D., Chicago, Ill.

POLYCYSTIC DISEASE OF THE KIDNEYS IN A NEWBORN INFANT.

By Benjamin P. Clark, M.D., and Amos C. Gipson, M.D., Gadsden, Ala.

EARLY WHOOPING COUGH IMMUNIZATION.

By Salmon R. Halpern, M.D., Ph.D., and Doris Halpern, Dallas, Texas.

THE TREATMENT OF TUBERCULOUS MENINGITIS.

By Leonard Alperin, M.D., and John A. Toomey, M.D., Cleveland, Ohio.

CHILDHOOD MANIFESTATIONS OF ALLERGIC ADULTS. PRELUDE TO ALLERGY.

By Abraham B. Schwartz, M.D., Milwaukee, Wis.

THE IMPORTANCE OF PEDIATRIC AND SURGICAL CARE IN THE PREVENTION OF SELECTIVE SERVICE REJECTIONS.

By William H. Davis, Jr., M.D., and Jay M. Arena, M.D., Durham, N. C.

PULMONARY CALCIFICATION IN TWINS

By Lieutenant Gilbert Houston and Captain W. A. Steiger, Medical Corps, Army of the United States.

FURTHER EXPERIENCE WITH THE HYPONIA TOLERANCE TEST OF THE HEART IN CHILDREN.

By Edgar Mannheimer, M.D., L. E. Carlgren, M.D., W. Graf, M.L., Stockholm, Sweden.

GRAPHS OF THE HEAD CIRCUMFERENCE OF THE NORMAL INFANT.

By Henry K. Silver, M.D., and William C. Deamer, M.D., San Francisco, Calif.

CONGENITAL TOXOPLASMOSIS.

By Joseph Schwartzman, M.D., Anthony Maffia, M.D., Margaret E. Crusius, M.D., and Andrew Brunhoffer, M.D., New York, N. Y.

RUPTURE OF LIVER AND SPLEEN IN THE NEWBORN INFANT.

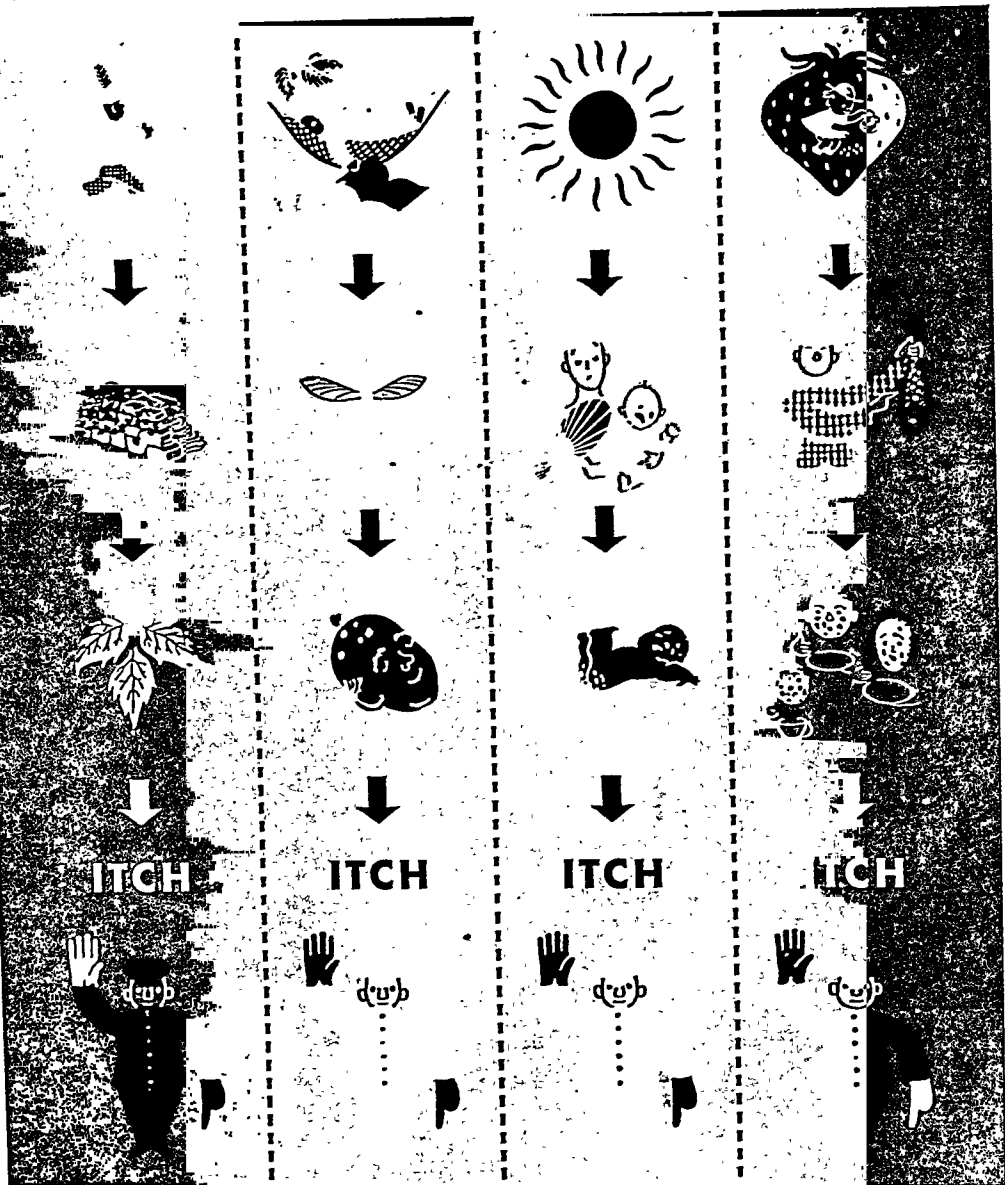
By Peter Gruenwald, M.D., Brooklyn, N. Y.

CONGENITAL GOITER CAUSING DEATH OF A NEWBORN INFANT.

By Ralph H. Kunstadter, M.D., Chicago, Ill.

FURTHER OBSERVATIONS CONCERNING HYPOFUNCTION OF THE ADRENALS DURING EARLY LIFE. INSUFFICIENCY OF THE DESOXYCORTICOSTERONE FACTOR.

By Joseph C. Jaudon, M.D., St. Louis, Mo.



CALMITOL

Thos. Leeming & Co. Inc.

155 EAST 44TH STREET, NEW YORK 17, N. Y.

Rx

a better lease on life

...with the dietary support of citrus fruits!

"Fully adequate nutrition permits optimum growth";⁴ and one of the most essential nutritional factors in childhood is vitamin C.

Its influence on calcium retention,¹ and its participation in the collagenous reinforcement² of intercellular substance,⁵ are the basis for its nutritional impetus to growth, stamina,³ and bodily vigor.⁸

Florida citrus fruits and juices (fresh or canned)—with their bountiful supply of vitamin C and other essential nutrients*—help assure "fully adequate nutrition" for younger patients. Children invariably like their tart, refreshing goodness, and lagging appetites,¹ slow digestion,⁶ and intestinal stasis,⁷ often respond to their mild stimulus. Their rich fruit sugars—easily assimilated for quick energy-release—render them ideally suited to the pediatric diet.

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA

References

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FLORIDA

Oranges • Grapefruit • Tangerines •

life...



Citrus fruits are among the richest known sources of vitamin C; they also contain vitamins A, B₁, G and P, and other nutritional factors such as iron, calcium, citrates, citric acid and readily assimilable fruit sugars.

DA
riness
of P...

May, 1948

Page 5

Use the safest antihistaminic first...

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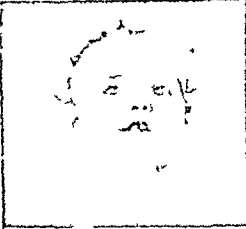
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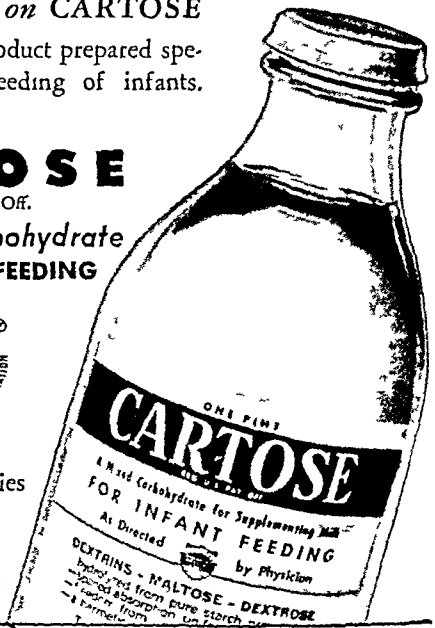
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Original Communications

THE RADIOGRAPHIC APPEARANCE OF THE GASTROINTESTINAL TRACT DURING THE FIRST DAY OF LIFE

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BELATED recognition of intestinal obstruction in the newborn infant due to congenital atresia, stenosis, malrotation, and bands lessens the chances for successful surgical intervention. The characteristic radiographic findings of pronounced distention of stomach or bowel with extensive fluid levels unfortunately portray the late phases of obstruction when the infant's condition is indeed precarious. To investigate a basis for earlier recognition, we undertook to determine the pattern of distribution of air in the gastrointestinal tract during the first day of life. The presence of air within the stomach of a living infant immediately after birth is demonstrated by Dillon¹ to be a constant finding. A survey of the available literature fails to disclose any investigations which describe the progression of this air.

Radiographic examination of fifty normal newborn infants was conducted either at the delivery floor or in the nurseries. Plain film studies were made with the infant in the supine position. Factors used were 38-40 kv., 30 Ma., 36 inch target-film distance, par-speed screens.

While it might be desirable for purposes of such a study to follow a group of infants in serial fashion during the first twenty-four hours, this was not feasible. We felt that the same information might be obtained if the number of newborn infants examined at various hours of life were sufficient.

Upon admission to the nurseries, effort is made to keep the newborn infants on their side for at least six hours. Thereafter, they lie in the prone position. The first feeding of 5 per cent glucose water is given eight hours after delivery. Subsequent feedings of evaporated milk mixtures are given at four-hour intervals.

IDENTIFICATION OF DIVISIONS OF THE GASTROINTESTINAL TRACT

The stomach is seen in the left hypochondrium and is generally elliptical in shape. Its upper border lies approximately one interspace below the left diaphragm. When the antrum is filled with air, it lies immediately to the right of the bodies of the twelfth dorsal and first lumbar vertebrae. The size of the stomach varies up to a maximum of 7 by 4 cm. The average measurements at

¹From the radiologic service of the Jewish Hospital of Brooklyn.

the eighth hour are 4.5 by 2 cm. Prior to this hour and also in the latter part of the first day, the stomach tends to be somewhat smaller, averaging 3.5 by 2 cm. in dimensions.

Air is visualized in the proximal portions of the small bowel in seven infants of the group of ten studied within the first hour after birth (Fig. 1, *B*). The pattern is a discontinuous one, and air-filled segments of bowel vary in length from 0.6 to 2.0 cm., and are approximately 0.6 cm. in width. These loops are found in the left half of the abdomen. Shadows, similar in mensuration but distributed throughout the abdomen, are noted in most infants older than one hour. These, we believe, represent the small bowel. In the absence of discernible circular folds, differentiation between jejunum and ileum is not possible.

The differentiation of large from small bowel we believe to be possible without barium meal studies. Henderson states, "The caliber of the ileum and of the colon with an opaque meal is apt to be so nearly the same, that . . . in many cases it is only when the barium is seen in the rectosigmoid that the examiner is certain that he has been observing barium-filled segments of colon and not ileum."² If air within the colon is insufficient to inflate the arms and flexures appreciably as in Fig. 1, *C*, identification of large bowel may prove difficult. This, however, is the exception. In newborn infants after the third hour of life, air-filled segments of greater caliber than small bowel are readily visualized in the flanks, within the true pelvis, and occasionally lying transversely in the upper abdomen. These measure 1.0 to 1.5 cm. in width. Increased radiolucency of these segments assists in their recognition as large bowel. In no instance is the colon visualized in its entirety. The ascending and descending arms are outlined in almost all instances after the third hour of life (Fig. 1, *E*). Haustral markings are generally indistinguishable, although in six infants they could be recognized as shallow and incomplete indentations.

Within three to eight hours after birth, a variable amount of air is seen within the true pelvis. Inasmuch as these shadows suggest large bowel characteristics, it is felt that they represent sigmoid and rectum. In many instances, the rectum itself can be identified by its conical termination. When positive delineation of the rectum is required, radiographs should be taken with the infant inverted.³

SEQUENCE OF FILLING OF THE GASTROINTESTINAL TRACT

The distribution of air observed in each of the newborn infants studied is represented schematically in Table I. From this tabulation it is evident that the sequence of filling of the divisions of the gastrointestinal tract follows a rather well-defined pattern. The timetable of passage of air is a fairly constant one.

Air is present in the stomach promptly after birth. Within the first hour, the proximal portion of the small bowel is outlined. Between the first and third hours, the remainder of the small bowel fills, and segments of large bowel first appear. The distal portions of the colon may be visualized as early as the third hour. From the fourth to eighth hour, there is a progressive increase in the amount of air distributed in both small and large bowel. At the eighth hour,

the striking finding is the presence of innumerable air-containing segments of small bowel, closely packed and filling the abdominal cavity, in contrast to the relatively lesser amount in the colon.

Following the first feeding, at the eighth hour of life, the relative proportion of air in the small as compared to the large bowel changes in favor of the latter. Segments of air-filled lesser bowel become fewer in number, poorly defined, and widely separated. By contrast the limbs of the colon become more prominent. At the twelfth hour, this distribution becomes established and continues as the characteristic pattern to the end of the first day of life.

COMMENT

It is well recognized that one cannot interpret x-rays of pathologic states without a thorough knowledge of the nuances of shadows that are found under normal conditions. Since the use of a barium meal is undesirable in many studies, the value of familiarity with the gaseous pattern of the gastrointestinal tract is readily understandable. Utilizing standards of mensuration and rate of dispersion of air in the bowel as described in this study, there should be less difficulty in determining the presence of dilated segments of bowel with a pattern of distribution of air inconsistent with the age of the newborn infant.

Clinical recognition of intestinal obstruction is rarely accomplished before the sixteenth to nineteenth hour of life. This study, however, suggests a procedure for earlier diagnosis. At the third hour of life, when ingested air normally traverses the small bowel and extends into the colon, it should be possible by plain film study of the abdomen to identify a disturbance in continuity of the intestinal tract.

CASE REPORTS

CASE 1.—W. B., a male infant, was delivered spontaneously at term without evidence of abnormalities. The first three feedings were well tolerated and meconium passed. At the *eighteenth* hour of life, the first episode of vomiting occurred. Physical examination revealed slight distention of the abdomen. Plain film studies at the twentieth hour (Fig. 1, K) disclosed evidence of lesser bowel obstruction.

Operation at another hospital revealed atresia of the small bowel at its mid-portion with absence of the mesentery in this area. The lumen of the proximal jejunal segment was found to be further occluded by a veil. A side-to-side anastomosis was performed.

The infant survived the surgical procedure but succumbed from other causes at a later date.

The blockage of air in the small bowel might have been determined by radiographic studies as early as the third hour of life well before the onset of clinical symptoms.

CASE 2.—B. F., a female infant, delivered spontaneously at term presented no evidence of abnormalities. Abdominal distention was noted *one* hour after birth. Vomiting occurred with the first feeding at the eighth hour of life. No stool was passed, but rectal examination disclosed no obstruction.

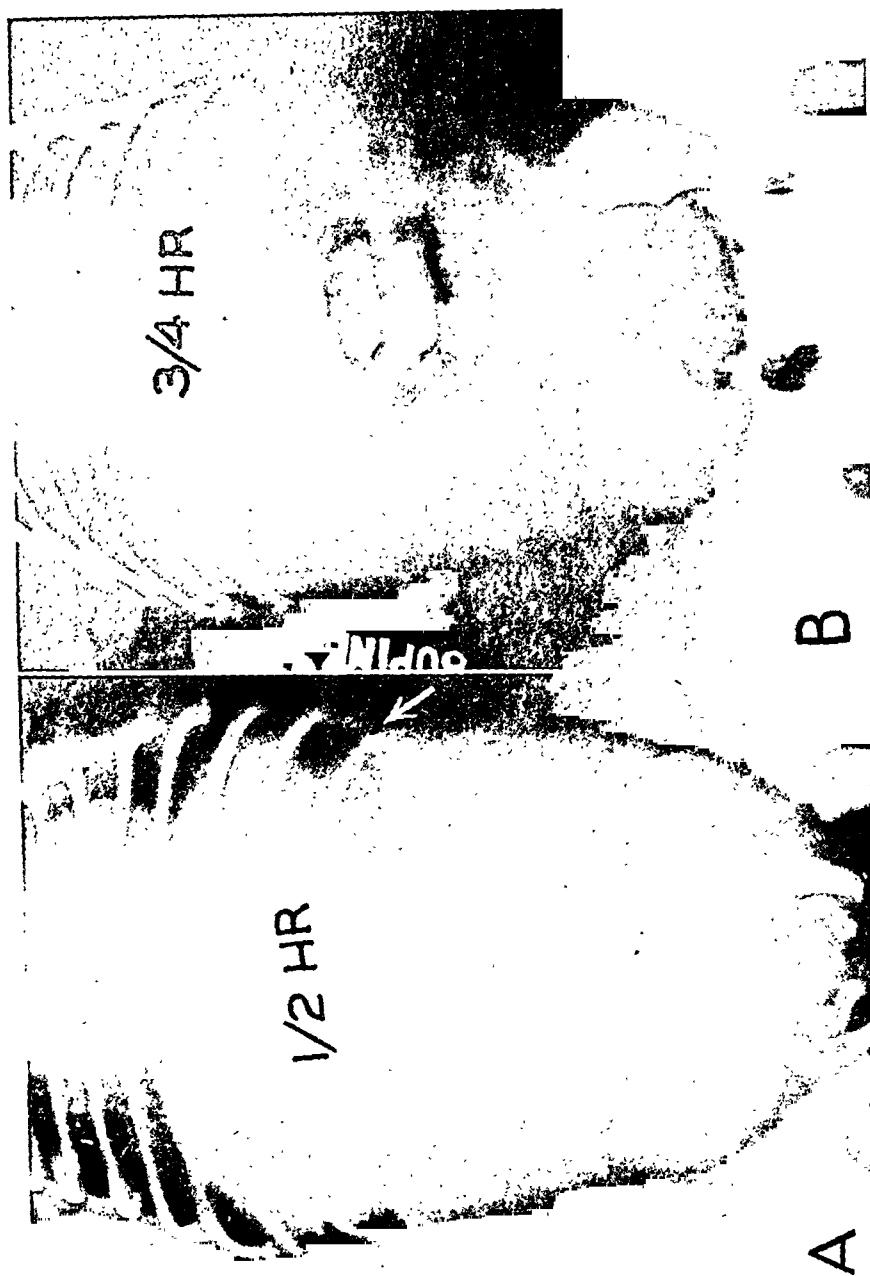


Fig. 1 A.—Normal infant at one-half hour after birth, revealing air in the stomach only (see arrow).
Fig. 1 B.—Normal infant, revealing air in stomach and jejunal coils three-quarters of an hour after birth.



Fig. 1 C.—At one and one-half hours after birth, there is a large amount of air distributed throughout the small bowel. Identification of segments in the flanks is questionable.
Fig. 1 D.—Normal infant at 3 hours of age, illustrating progression of air to distal portions of the colon. Amount of air in the small bowel is about the same as in C. Ascending and transverse arms are readily identified. Air present within the true pelvis is earliest instances in this series.

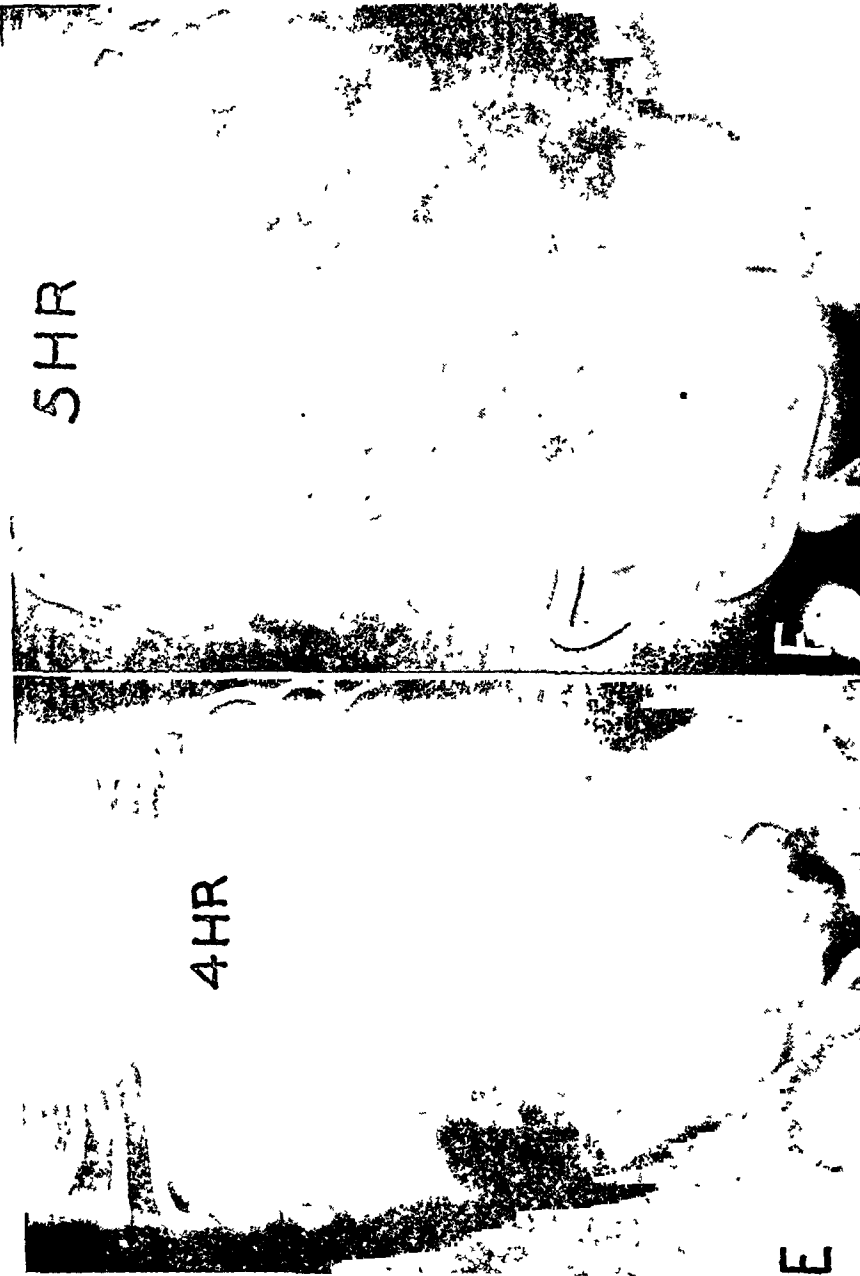


Fig. 1 *D*.—Four hours after birth, air-filled segments of small bowel are numerous. Discontinuous segments in right lower abdomen probably represent ileum. Hepatic flexure is well outlined. Some air is present in the descending colon.
 Fig. 1 *F*.—Normal infant at fifth hour after birth with well-inflated stomach, numerous small bowel segments, and prominent and redundant distal colon.

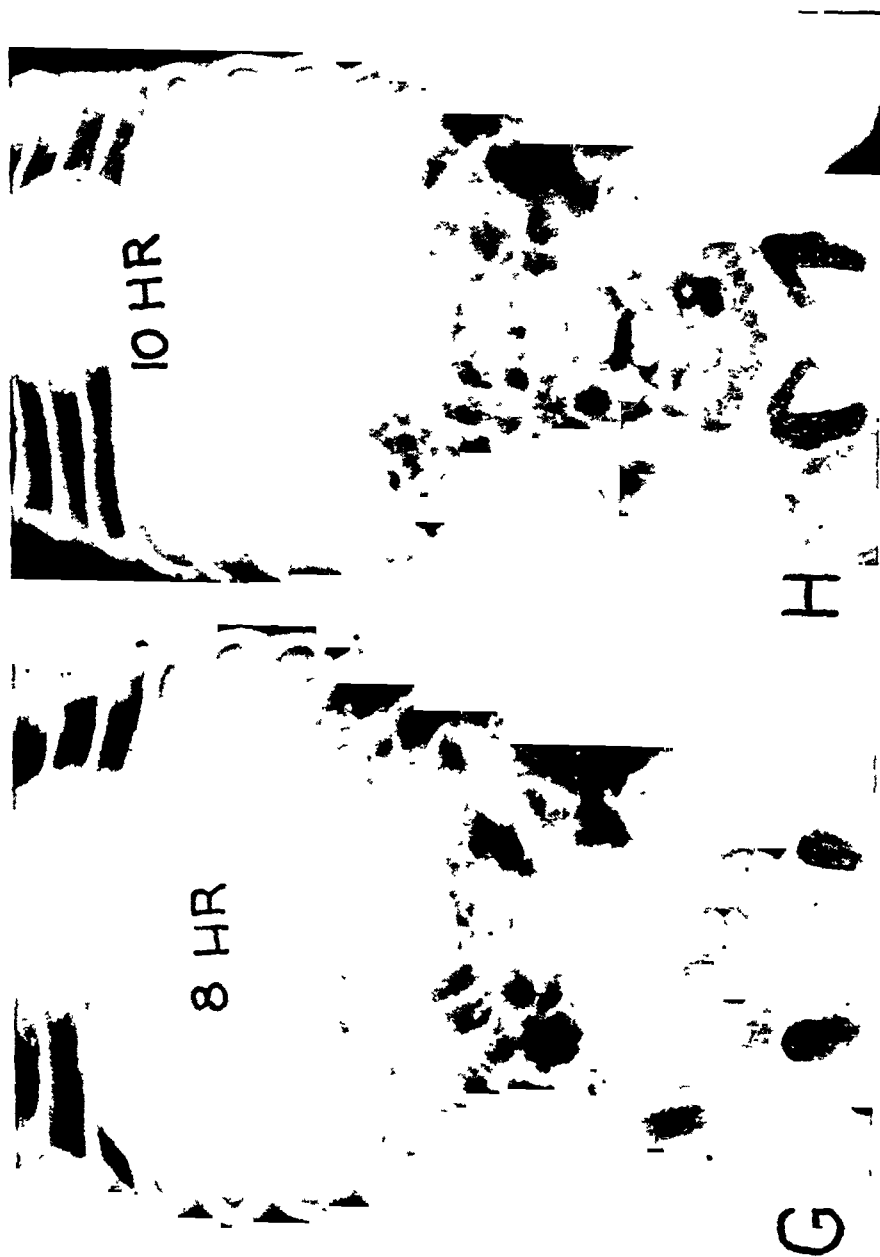


Fig. 1 G—Normal infant at eighth hour of life, demonstrating maximum dispersion of air through the small bowel. Ascending and pelvic colon are well patterned.
 Fig. 1 H—At tenth hour, air is disseminated throughout the lesser bowel and colon but is slightly less prominent than at eighth hour.

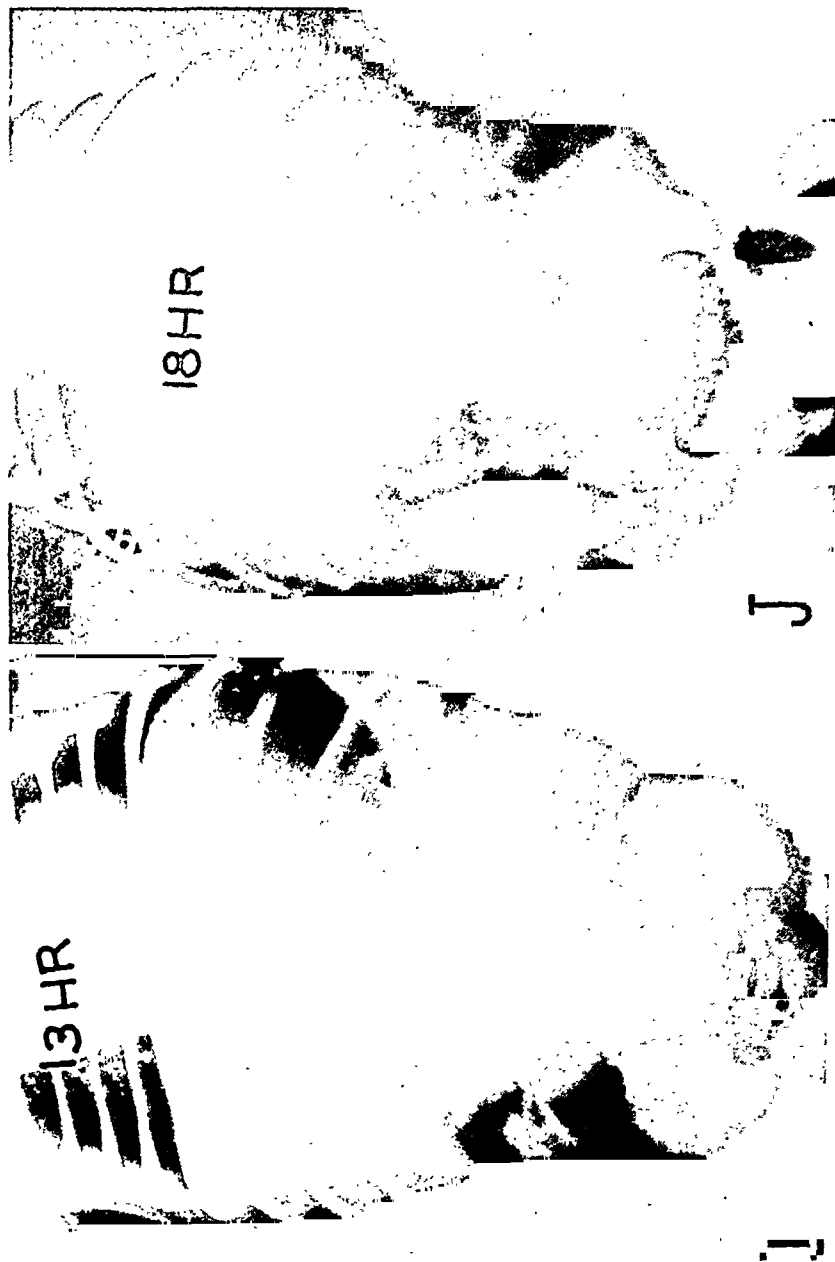


Fig. 1 *I*.—Normal infant at thirteenth hour of life showing further decrease in amount of air in the small intestine. Visible segments are few in number, widely separated, and poorly defined. Air present in stomach from recent intake.

Fig. 1 *J*.—Eighteen-hour-old infant, revealing usual appearance in latter half of first day of life.

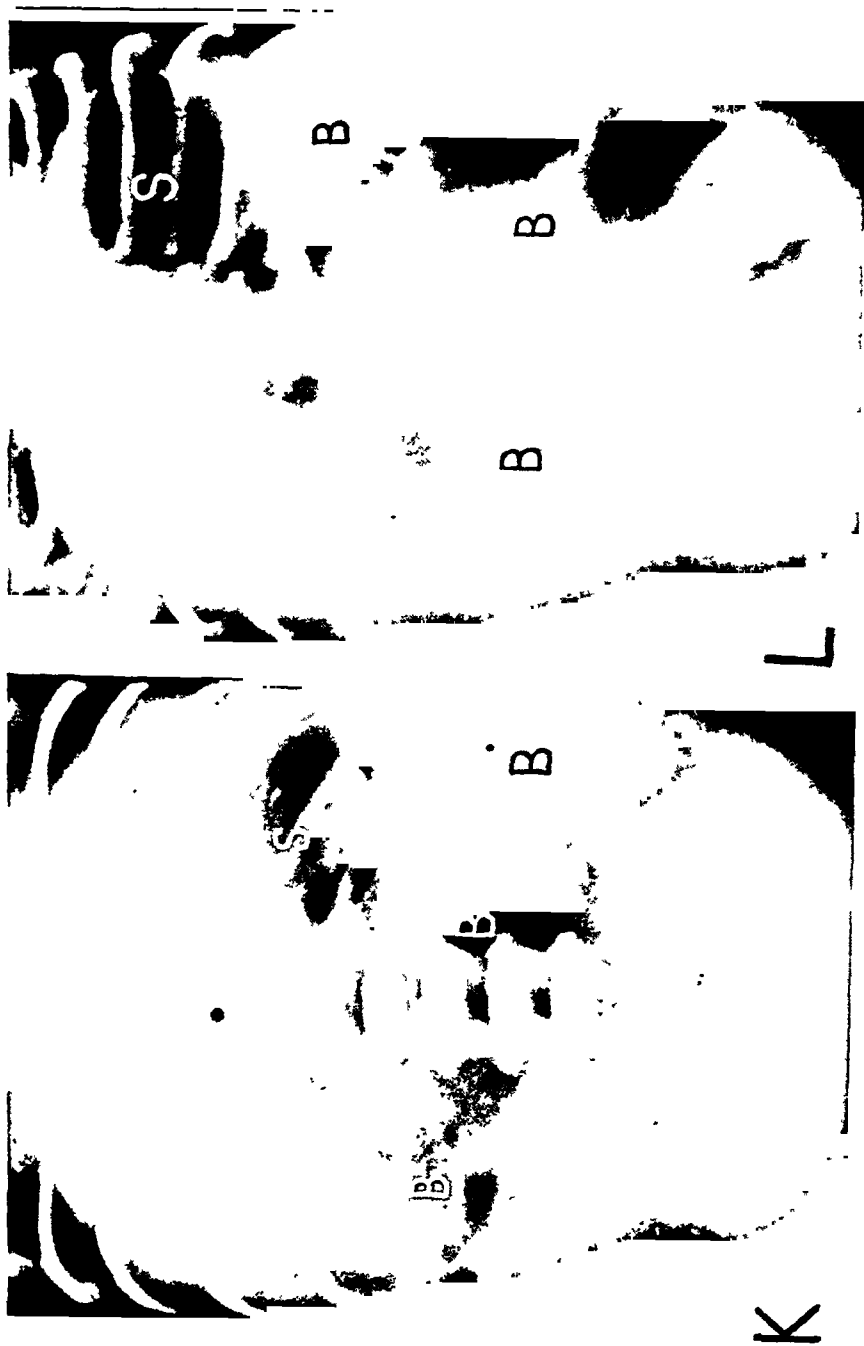


Fig. 1 K—(Case 1.) Supine study at twentieth hour of life reveals stomach (S) to be within normal limits. A segment of small bowel (B-B) lies across the midabdomen and measures 6×10 cm. Several smaller and less distended segments are found in the right and lower abdomen. The large bowel is not visualized. Diagnosis: Small bowel obstruction.

Fig. 1 L—(Case 2.) Supine study at thirty-sixth hour of life shows the stomach (S) to be large, measuring 6×3 cm. Several distended coils of small bowel (B-B) measuring 2 cm. in width lie obliquely in the left abdomen. These segments vary in length up to 5.5 cm. Normal small bowel segments do not exceed 0.6 cm. in width and 2.0 cm. in length. The large bowel is not visualized. An erect study, not illustrated, revealed fluid levels in the left abdomen. Diagnosis: Small bowel obstruction.

TABLE I. DISTRIBUTION OF AIR IN THE GASTROINTESTINAL TRACT OF NEWBORN INFANTS

CASE NO.	AGE IN HOURS	SEX	STOMACH	SMALL BOWEL	LARGE BOWEL			SIGMOID &/OR RECTUM
					ASCEND-ING	TRANS-VERSE	DESCEND-ING	
31	1½	M	++	0	0	0	0	0
37	1½	M	++	0	0	0	0	0
38	1½	F	++	+	0	0	0	0
29	1½	M	++	+	0	0	0	0
33	1½	F	++	+	0	0	0	0
35	¾	F	++	0	0	0	0	0
32	¾	F	++	+	0	0	0	0
36	¾	M	+++	+	0	0	0	0
34	¾	M	+	++	0	0	0	0
30	¾	M	++	++	0	0	0	0
47	1½	M	++	++	?	0	0	0
9	1½	M	+	+++	?	0	?	0
27	2	F	+++	++	0	0	0	0
14	2	F	++	++	+	0	0	0
19	2	M	++	+++	++	0	0	0
56	2	M	++	++	+	?	?	0
28	3	F	+	+++	+	++	+	+
20	4	F	+++	+++	++	0	+	0
1	5	F	+++	+++	+	0	+++	0
48	5½	F	++	++	+	+	++	0
10	6	M	+	++	++	++	++	+
52	7	F	++++	+++	++	0	++	0
4	8	F	+++	++	+	0	+++	0
12	8	F	+++	++++	++	+	++	0
26	8	M	++	++++	+	0	+	+
11	8	F	+++	++	0	0	+	+
21	8	F	++	++	+	0	++	+
25	8	M	+++	+++	+++	+++	+++	+
24	8	M	++	++++	++	0	+	++
22	9	F	+	+++	+++	0	+++	+++
43	9	F	++	++++	++	0	++	+
18	10	M	+	+++	+	0	+	+
15	12	F	+	+	+	0	++	0
3	12	F	++	0	++	+	+	++
17	13	M	++	+	++	++	++	+
16	13	M	++	+	+	0	+	+
55	13	F	+	+	+++	0	0	++
42	14	M	+	+	++	0	++	+
54	16	F	++	++	++	+	++	0
40	16	M	+	+	+	0	+	+++
6	16	F	++	+	++	0	++	+
41	17	F	++	+	++	0	0	+
44	17	M	++	+	+++	?	++	++
13	18	M	++	+	+	0	++	+
23	18	F	+	++	++	0	0	0
7	19	F	++	+	+	0	+	++
5	20	M	+	++	+	0	+++	++
50	20	F	+	+	++	0	+	++
53	24	F	++	+	+++	0	+++	+
57	24	F	++	+	+++	+	+	+

Radiographic studies at the *thirty-sixth* hour of life (Fig. 1, *L*) presented evidence of complete intestinal obstruction involving the proximal portion of the small bowel.

Operation revealed a congenital peritoneal band at the jejunoileal junction with atresia of the bowel in this region. A side-to-side anastomosis was performed. The infant survived the surgical procedure but failed to improve and succumbed at the fifty-fourth hour of life.

The progression of air through the small bowel during the first hour of life is confirmed by the time of onset of distention in this instance. Radiographic studies at the third hour of life might have obviated the delay before surgical intervention, with the possibility of a successful result.

CONCLUSIONS

1. Fifty normal newborn infants were examined at varying hours during the first day of life.
2. Average dimensions and appearances of the divisions of the gastrointestinal tract are described.
3. Plain films reveal a characteristic pattern of the passage of air through the gastrointestinal tract which may be correlated with the hour of life of the infant.
4. Radiographic studies at the third hour of life are suggested as a "screening" procedure in all cases held suspect for intestinal obstruction.
5. Two case reports are given as illustrations to demonstrate the application of this type of study to pathologic states.

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THE USE OF BENZEDRINE AND DEXEDRINE SULFATE IN THE TREATMENT OF EPILEPSY

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BALTIMORE, Md.

UNTIL the discovery by Putnam and Merritt¹ in 1937 of dilantin, a non-sedative anticonvulsant, epileptic drug therapy had consisted almost exclusively of the two sedative drugs, bromide and phenobarbital. In addition to its clinical value, the discovery of dilantin is important because it demonstrates the fact that sedative action is not a necessary requisite of an anticonvulsant drug.

Even before the introduction of dilantin, it had, in a very limited manner, been observed that certain nonsedative drugs such as strychnine, caffeine, thyro'd, ephedrine, and theocalcin favorably affected the course of some epileptic patients. Benzedrine Sulfate had also been used, but mainly to counteract undesirable reactions of sedatives.²⁻⁵

The work described in this paper was prompted by the results obtained on two patients who were being followed in our epilepsy clinic. One was a 14-year-old white boy who had suffered with epilepsy since he was 5 years of age. He had daily petit mal spells (simple staring type) and two or three short grand mal convulsions weekly. Physical examination was essentially negative except for a dull, phlegmatic disposition and a marked postural hypotension (marked decline in systolic blood pressure after changing from recumbent to an erect position). The other patient was a 13-year-old white girl who had suffered for about ten years with frequent petit mal spells of the myoclonic variety. She presented the same type of disposition and postural hypotension. Both of these patients had been treated with the usual form of drugs without benefit.

It was intended to administer to these two patients a drug or group of drugs which might correct the hypotension and sluggishness and thus, through its general effect, influence the seizures indirectly. Since benzedrine sulfate not only possesses a vasopressor effect but also stimulates the central nervous system, both patients were started on 5 mg. of this drug daily, and the dosage was increased 5 mg. per day every two weeks until they were receiving 25 mg. daily. At this point a marked decrease in the frequency of the spells was noted in both patients, particularly in the petit mal spells. The blood pressure, however, was not affected in either instance, probably because of the relatively small amount of benzedrine sulfate employed, but there was some improvement of the disposition in each case. The anticonvulsant effect of the benzedrine was so striking that the drug was deemed worthy of further trial on all types of epileptic patients, regardless of their physical or mental make-up.

From the Department of Pediatrics of the Johns Hopkins University Medical School and the Epilepsy Clinic of the Johns Hopkins Hospital.

This study was supported, in part, by the Lederer Fund for the Study of Epilepsy.

The Benzedrine and Dexedrine Sulfate used in this study was supplied by the Smith, Kline and French Laboratories, Philadelphia, Pa.

MATERIAL FOR STUDY

This study comprises a group of eighty-five patients of the Epilepsy Clinic of the Johns Hopkins Hospital who were treated with benzedrine sulfate or its dextrorotatory component, Dexedrine Sulfate. Approximately one-half of these patients did not respond to the usual forms of therapy, not including tridione which was not available at the time of this study. The remainder of the patients had received no other forms of medication.

Fifty-one patients suffered from idiopathic epilepsy and thirty-four from organic epilepsy. Twenty-eight had pure petit mal spells (simple staring, myoclonic or akinetic types), eighteen had grand mal seizures, and thirty-nine had a combination of both types of seizures.

Seventy-seven of the patients ranged in age from 2 to 14 years, and eight from 14 to 21 years.

DURATION OF TREATMENT

The patients were observed for periods varying from two months to five years. In twenty-six patients, the medication was discontinued after two months because it proved to be ineffective. In four, the drug was stopped after six months because of toxic reaction in two individuals, poor cooperation in the third, and ineffectiveness in the fourth. Sixteen patients received the drug from six to twelve months, and forty-nine from one to five years, the average duration of treatment in the entire group being eighteen months.

DOSAGE

Seventeen of the patients were treated with either benzedrine sulfate or dexedrine sulfate alone, while to sixty-eight the drug was administered in combination with phenobarbital.

The daily dosage of benzedrine sulfate prescribed varied from 5 to 45 mg. Generally, to the younger children (under 6 years of age) the initial dosage of 2.5 mg. twice daily was increased until satisfactory therapeutic results were obtained. The total daily dose was not permitted to exceed 10 mg. In the older group the daily dose varied from 7.5 to 45 mg. When dexedrine sulfate was employed, the daily dosage for the younger children was between 2.5 and 5 mg. daily, and for the older group, between 5 and 15 mg. daily. When the larger quantities were employed, the medication was administered in three or four doses over the course of the day, the last usually at 4 P.M., never later than 6 P.M.

RESULTS

For the purpose of this study, improvement was scored as:

1. Controlled, when there was no recurrence of seizures during the entire observation period.
2. Markedly improved, when the frequency of seizures was reduced to less than one-fourth of the previous frequency.
3. Improved, when the number of seizures became less than one-half.
4. Failure, when the number of seizures were only slightly reduced or the status remained the same or the condition became worse.

TABLE I. RESULTS OF BENZEDRINE SULFATE AND DEXEDRINE SULFATE TREATMENT WITH RESPECT TO TYPE OF EPILEPSY

TYPE OF EPILEPSY	NO. PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Idiopathic	51	21	8	2	20
Organic	34	11	7	0	16
Total	85	32	15	2	36

TABLE II. RESULTS OF BENZEDRINE SULFATE AND DEXEDRINE SULFATE TREATMENT WITH RESPECT TO TYPE OF SEIZURE

TYPE OF SEIZURE	NO. PATIENTS	CONTROLLED	MARKEDLY IMPROVED	IMPROVED	FAILURE
Petit mal	28	14	5	1	8
Grand mal	18	2	3	0	13
Mixed	39	16	7	1	15
Total	85	32	15	2	36

Of the 85 patients treated, 32 were controlled, 15 markedly improved, 2 improved, and in 36 the treatment was considered a failure.

The results of the treatment with respect to the type of epilepsy and the type of seizure are shown in Tables I and II.

It will seem there is no significant difference in the outcome of the idiopathic group as compared with the organic group, although generally the seizures of idiopathic epilepsy are more amenable to drug therapy.

It will be seen in Table II that the drugs are most effective in controlling the spells of petit mal epilepsy. Five of the seven patients reported as markedly improved in the group of thirty-nine patients with the mixed type of spells were completely relieved of their petit mal spells, but the grand mal convulsions were unaffected.

ELECTROENCEPHALOGRAPHIC STUDY

During the course of this study, electroencephalograms were done on 52 of the 85 patients. The brain wave pattern of 1 patient was considered to be within normal limits. This patient suffered with grand mal epilepsy, and the seizures were not influenced by the drug. Eight patients revealed essentially normal waves in the resting pattern and spike and waves only on hyperventilation. Of these, 2 were controlled, 1 was markedly improved, and 5 were failures. Nine patients showed three-per-second waves in the resting pattern. Of these, 4 were controlled, 1 was markedly improved, 1 was improved, and 3 were failures. Twenty-nine presented the classical three-per-second spike and wave pattern of petit mal epilepsy which was present in the resting state. Of these, 15 were controlled, 6 were markedly improved, and 8 were failures. Five patients presented fast spiky waves with evidence of localization. Of these, 2 were controlled, 1 was markedly improved, and 2 were failures.

These findings indicate that the more the brain wave pattern was characteristic of petit mal epilepsy, the more the drugs were effective in controlling the spells. However, the clinical improvement and that of the electroencephalographic pattern did not go parallel in each case. In 4 of the patients the seizures were clinically controlled without any improvement in the electroencephalogram. On the other hand, in spite of definite improvement in the brain wave pattern, in 5 patients the seizures were not significantly reduced.

TOXIC REACTIONS

The toxic side reactions observed were of a minor nature. The pulse and blood pressure were observed at regular intervals and remained essentially unchanged throughout the course of the treatment.

Two patients complained of insomnia, but this difficulty was relieved by changing the last dose of benzedrine from 6 P.M. to 4 P.M. Three of the patients showed a considerable loss of weight. This phenomenon was, however, concomitant with such a marked improvement in the clinical course that the treatment was kept up with two of the subjects. It was discontinued with the third because he manifested an undue amount of general weakness. Increased irritability and restlessness, which were noted in four instances, were controlled in two by reduction of the dosage. Two patients had marked tremors of the hands. In one the drug had to be discontinued; in the other the tremor disappeared upon reducing the dose. In one patient a glycosuria was observed. The drug was discontinued for several weeks and started again, but the glycosuria did not reappear.

COMMENT

At the onset of this study, benzedrine sulfate alone or in combination with phenobarbital was used. Later, when benzedrine sulfate (d,l-amphetamine) was split into its two components, d-amphetamine (dexedrine sulfate) and l-amphetamine, each of the components was tried separately. The dexedrine sulfate proved to be as effective in controlling the spells as the benzedrine sulfate, whereas the l-amphetamine did not appear to possess an anticonvulsant power. The latter drug was tried upon ten patients not included in this study and proved to be ineffective in each case. The ineffectiveness of l-amphetamine as an anticonvulsant was reported by Tainter and his co-workers.⁶ They demonstrated that both benzedrine sulfate and dexedrine sulfate raised the convulsive threshold of rabbits, whereas l-amphetamine was almost completely inactive.

As has been previously mentioned, Cohen,² Cook and Dole,² and Robinson⁴ each used benzedrine sulfate in the treatment of epilepsy, but primarily to counteract the drowsiness caused by large doses of phenobarbital. Cook also observed that the addition of benzedrine sulfate significantly diminished the frequency of the seizures in six of his patients. These patients were all deteriorated epileptics, and no distinction was made as to the type of seizures. Strauss⁷ used benzedrine sulfate in the treatment of four epileptic children; two had petit mal spells and two had occasional grand mal seizures. He observed definite improvement in the two patients with petit mal spells. Both Cook and Strauss suggested that the beneficial effect of the benzedrine sulfate was due to an improvement of the mental state of the patients.

Turner and Carl⁸ administered benzedrine sulfate to a group of normal individuals in order to study the effect of the drug on the mental state. Their conclusions are as follows: "It is reasonably clear that in a majority of individuals benzedrine sulfate produces a definite heightening of mood, a fairly generalized optimism and interest together with an increased willingness to work for extended periods of time. In other individuals the same dosage had none of these effects, in still others, the opposite effects."

Since it is an established fact that a betterment of the disposition and attitude of an epileptic individual favorably influences the frequency of seizures, especially in petit mal epilepsy, and since the majority of our patients who improved clinically (cessation or decrease in number of seizures) also showed an improvement in general well-being, we agree with Turner and Carl that the beneficial effect of benzedrine sulfate is most likely due to a direct action on the cerebrum. The fact that the majority of our patients with petit mal epilepsy improved while others did not parallels the results obtained by Turner and Carl on normal individuals.

The study presented in this paper indicates that benzedrine or dexedrine sulfate is a useful drug in the control of petit mal epilepsy. No significant difference in the effectiveness of the drug was observed when it was used alone or in combination with phenobarbital. Since patients suffering with pure petit mal epilepsy are very prone later to develop grand mal convulsions also, it is deemed advisable to administer the combined therapy, the benzedrine to control the petit mal spells and another anticonvulsant such as phenobarbital or dilantin to attempt to prevent the grand mal seizures from "breaking through."

SUMMARY

1. Eighty-five epileptic patients, mostly children, were treated with benzedrine or dexedrine sulfate; the seizures were controlled in 38 per cent and markedly or moderately improved in 20 per cent.

2. These drugs were more effective in controlling petit mal than grand mal seizures.

3. There was no difference in the results in idiopathic and organic epilepsy.

The authors acknowledge their deep appreciation to Drs. Ruth W. Lidz and Orthello R. Langworthy for their interpretation of the electroencephalograms performed on the patients followed in this study.

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DIAGNOSIS AND SURGICAL TREATMENT OF CERTAIN CONGENITAL CARDIOVASCULAR ANOMALIES

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NO MORE noteworthy development has occurred in medicine in recent years than that pertaining to the surgical correction of certain congenital cardiovascular anomalies during the past decade. Successful surgical intervention in these cases has resulted in a more thorough and critical diagnostic analysis of every case of congenital heart disease with resultant increased precision of diagnostic methods. Unfortunately, much of this newer knowledge has not as yet been collected in a readily available source. It is the purpose of this paper to outline briefly the cardinal criteria of congenital cardiovascular anomalies now known to be amenable to surgical treatment.

PATENT DUCTUS ARTERIOSUS

Anatomy and Physiology.—The ductus arteriosus is a short vessel, 0.5 to 2.0 cm. in length, extending from the aorta to the left pulmonary artery. It is essential to the fetal circulation, carrying blood from the pulmonary artery to the aorta. At the end of the first week¹ of life about 0.75 per cent of ducti are estimated to have closed, and at the end of the first year this has increased to 95 per cent. If patency persists, an arteriovenous shunt results. With a compensating heart there is a continuous leakage of blood into the pulmonary artery from the aorta. Cyanosis is absent unless the pressure in the systemic circulation becomes very low, or the pressure in the pulmonary circulation becomes much increased; then transient cyanosis may appear.

Because of the shunt, the pressure in the pulmonary artery is increased with resultant dilatation. More blood is thrown into the left side of the heart with the left ventricle² expelling two to four times the volume of blood expelled by the right ventricle during the same period of time. Eppinger, Burwell, and Gross² also showed in their patients that 45 to 75 per cent of all blood pumped from the left ventricle into the aorta flowed through the shunt into the pulmonary artery. Additional burden is thrown on both the right and left ventricles with frequent hypertrophy of each.

Diagnosis.—Often the diagnosis is made during a routine physical examination in an otherwise well-developed child. Less frequently the child may appear small in stature, poorly nourished, and may complain of tiring easily. Occasional attacks of dyspnea, transient cyanosis, and palpitation may be noted. The most characteristic finding is a loud murmur, increasing in intensity throughout systole to a maximum at the time of the second sound and decreasing during diastole.³ It usually is continuous throughout both systole and diastole but may disappear during late diastole. The maximum intensity is in the second interspace just to the left of the sternum. With lessened intensity it

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may be transmitted over the whole precordium, left axilla, and to the back. A palpable thrill usually accompanies the murmur, and the second pulmonary sound is loud and snapping. It is important to note that in young children and infants the murmur may be entirely missing or be present only during systole.

Blood pressure levels will vary with the size of the shunt. When a large amount of blood is shunted through the ductus, the systolic level is normal or elevated and the diastolic level depressed with a resultant high pulse pressure. In addition, peripheral signs of aortic regurgitation are present. Following exercise the diastolic level becomes lower instead of the normal response of becoming slightly elevated. These signs vary in intensity in direct proportion to the size of the ductus.

Röntgen examination is most valuable in confirming the diagnosis. The heart is usually of normal or slightly enlarged size. Sometimes there is hypertrophy of the left ventricle. The pulmonary conus is dilated, and the lungs show vascular congestion. In some of the patients pulsation of the pulmonary arteries in the hilar regions of the lungs may be demonstrated. The electrocardiogram is either normal or may occasionally show some left axis deviation. (Fig. 1.)

Differential diagnosis.

1. *Interauricular septal defect:* Children with this defect may also show evidences of retarded physical growth and poor nutrition. A systolic murmur and thrill are present over the pulmonic area with an early diastolic murmur infrequently occurring due to dilatation of the pulmonary artery. The blood pressure reveals a normal pulse pressure, responds in a normal fashion to exercise, and peripheral signs of aortic regurgitation are absent. The electrocardiogram usually shows right axis deviation. On roentgen examination the heart is enlarged, with a prominent pulmonary conus, increased pulmonary vascular markings, and enlargement of the right auricle and ventricle, and the shadows of the ascending aorta and aortic knob are very small or absent.⁴ (Fig. 2.)

Direct catheterization of the heart should reveal a higher oxygen saturation of blood from the right auricle than that from the superior vena cava. In an uncomplicated patent ductus the oxygen saturation would be either the same in both or slightly higher in the superior vena cava.

Angiocardiography⁵ will reveal an atrial septal defect. Occasionally a right-to-left shunt will be seen with immediate opacification of the left auricle following the right. Usually a left-to-right shunt can be demonstrated by continued opacification of the right auricle beyond the time it should have cleared.

2. *Interventricular septal defect:* This is less likely to be confused due to the different character of the murmur which is systolic in time and heard best over the third and fourth interspaces, just to the left of the sternum. It is frequently accompanied by a systolic thrill. The roentgenogram usually reveals an enlarged right ventricle and pulmonary conus. The ventricular enlargement pushes the apex of the heart up off the diaphragm. The electrocardiogram usually shows a deep S wave in Leads I and II.

3. *Localized defect of the aortic septum:* In this condition there is a communication between the first portion of the ascending aorta and the pulmonary

artery or between one of the aortic sinuses of Valsalva and the base of the right ventricle near the level of the pulmonary valves. A loud, coarse, "machinery-like" murmur is present throughout both systole and diastole, accompanied by a thrill. The murmur and thrill are very superficial and have their maximum intensity in the third and fourth interspaces just to the left of the sternum.⁶ A wide pulse pressure and peripheral signs of aortic regurgitation are present.⁷



Fig. 1.

Fig. 1.—Patent ductus arteriosus.

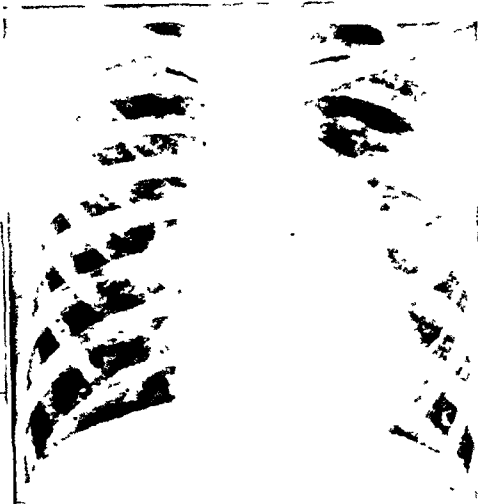


Fig. 2.

Fig. 2.—Interauricular septal defect.

4. *Pulmonary stenosis*: This is infrequently found alone, usually being associated with a combination of defects constituting the tetralogy of Fallot. Persistent cyanosis is constant in the latter but may be absent in the former. In the absence of cyanosis, the distinguishing features of an uncomplicated pulmonary stenosis are a systolic murmur with maximum intensity at the pulmonic area and a weak or absent pulmonary second sound. Clubbing is almost always present. Right axis deviation and high P waves are seen in the electrocardiogram. There is enlargement of the right auricle and ventricle. The stenotic segment may be demonstrated by angiocardiography. Roentgen examination reveals the pulmonary conus to be small or absent, the hilar vascular shadows very light, and absence of hilar arterial pulsations.

Surgical Treatment of Patent Ductus Arteriosus.—Surgical obliteration of a patent ductus arteriosus was first suggested in 1907 by Munro⁹ and first attempted by Strieder⁸ in 1937. In Strieder's case, complicated by subacute bacterial endarteritis, death occurred on the fourth postoperative day. The first successful ligation of a patent ductus arteriosus was reported by Gross¹⁰ in 1939, after which, within a very short time, numerous successful ligations were recorded, and the operation quickly became an established procedure. In competent hands the operation today has a very low mortality. In the last twenty cases of patent ductus arteriosus at Barnes and the St. Louis Children's Hos-

pitals, ligations have been carried out with no deaths and with no postoperative complications.

Gross^{11a} has lately recommended transection and suture of the ductus as a better procedure than simple ligation. In our hands ligation by a double ligation transfixion technique has not been complicated in a single instance by recanalization. We are, therefore, not enthusiastic about a procedure which inescapably increases the operative risk.

To Touroff¹² belongs the credit for showing that bacterial endarteritis is not a contraindication to the operation but on the contrary is an indisputable and urgent indication.

Considerable divergence of opinion still exists concerning indications for operation in cases of patent ductus arteriosus. Our own feeling is that the operation is indicated in all age groups when the condition is associated with bacterial endarteritis or with evidence of impending heart damage. In those cases which are uncomplicated we advise operation on virtually all patients between 3 and 18 years of age. These age limits are more or less arbitrary and require some explanation. It is our feeling that beyond the age of 3 there is very little chance of spontaneous obliteration of a patent ductus. On the other hand, if a patient survives past adolescence without evidence of cardiac damage, developmental retardation, or subacute endarteritis, that case would seem to warrant individual evaluation. In the group between the ages of 3 and 18, there seems to be no valid reason to deny them the benefit of a rational prophylactic procedure which can be done in proper hands with a mortality rate considerably less than the risk of the disease itself.

COARCTATION OF THE AORTA

Anatomy and Physiology.—Coarctation of the aorta is, by definition, a condition in which there is a constriction of the aorta, usually in the descending portion. Cases of this condition are classified as adult or infantile. In the former, the constriction is localized at, or just distal to, the insertion of the ductus arteriosus, which is usually closed. The infantile type is a more generalized narrowing of the aorta, extending to the insertion of the ductus arteriosus, which is usually open, providing free passage of blood from the pulmonary artery directly into the descending aorta, beyond the point of constriction. Associated congenital abnormalities, except for bicuspid aortic valves, are unusual in the adult type but more common among the infantile group, sometimes causing death early in the neonatal period.

The collateral circulation¹ is very extensive in the adult type with the usual channels being the superior intercostal artery anastomosing with the first aortic intercostal artery; the posterior scapular, infrascapular, and subscapular arteries anastomosing with the second intercostal artery; and the internal mammaries anastomosing with the epigastric and iliac arteries. The same situation does not obtain in the infantile type. If the theory is correct that the coarctation is present in utero, the location of the narrowing is undoubtedly of great importance in the development of an adequate collateral circulation. In the normal fetus, most of the blood flow in the pulmonary artery is shunted through

the ductus arteriosus to the descending aorta. It can readily be seen (Fig. 3, *A*) that with the adult type of coarctation the narrowing would still be distal to the entrance of blood into the aorta, while with the infantile type (Fig. 3, *B*), the blood flows from the ductus arteriosus into the descending aorta without encountering the constriction. It is, therefore, probable that even at this stage of development in the adult type, relative hypertension exists in the pulmonary artery and proximal aorta. In the infantile type, however, there would be no such hypertension in the pulmonary artery, and although it would be present in the proximal aorta, it would undoubtedly be less marked than in the adult type. On the basis of need, collateral circulation would be expected to develop much more extensively before birth in the adult type than in the infantile.

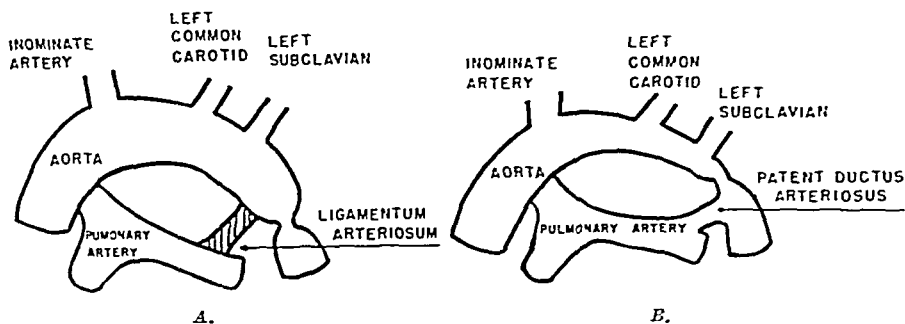


Fig. 3.—Coarctation of the aorta: *A*, adult type; *B*, infantile type.

Shortly after birth, with closure of the ductus arteriosus, the infant with the adult type would have an already formed collateral circulation, while the child with the infantile type would have very little. Not being able to form this collateral circulation as rapidly as the ductus closes, the child would be suddenly left with no route for arterial blood to escape from the heart except through the very narrow aorta. The pressure in the proximal aortic segment would rise rapidly, and he would be precipitated into fatal cardiac failure.

The adult type has been studied most extensively. There is hypertension in the head and upper extremities with hypotension (primarily systolic) in the rest of the body. Where collateral circulation is very abundant, the diastolic blood pressure readings in the lower extremities are frequently as high or higher than those of the upper extremities,¹² indicating a general peripheral resistance in addition to that of the coarctation itself. Of some diagnostic importance is the appearance¹ of the capillaries, which can be visualized in certain areas of the skin by a microscope. In the upper extremities minute capillary aneurysms may be seen, while the capillaries of the lower extremities present a normal appearance. The heart at rest maintains a normal or increased volume output of blood before the onset of failure.

Diagnosis.—

1. *Adult type:* During the early years of life there are usually no specific symptoms which can be attributed directly to the coarctation. The child usually appears healthy, vigorous, and may be quite athletic. Occasionally,

there are complaints of headache, dizziness, epistaxis, coldness and tingling of the feet, and intermittent claudication. With the onset of cardiac failure there are, in addition, dyspnea, palpitation, and precordial pain. Physical examination may reveal enlarged arteries over the scapular, interscapular, and clavicular areas. Thrills and bruits may be heard over these same areas. The heart sounds are usually normal, but often there is a systolic murmur best heard just to the left of the spinal column, in the interscapular area. Anteriorly, this is sometimes heard to the left of the sternum, in the second and third interspaces. Radial pulsations in the upper extremities are strong and forceful in contrast to the usually weak or absent pulsations of the femoral arteries and dorsalis pedis. Blood pressure readings reveal a hypertension in the upper extremities and a low blood pressure, which frequently cannot be obtained, in the lower extremities. In about 5 per cent of cases the diagnosis is missed because the blood pressure in the upper extremities is normal, or the pulsations in the femoral arteries will not be diminished. Not infrequently the blood pressure in the right arm will be higher than the left, with correspondingly stronger radial pulsation. This is primarily due to a more diffuse narrowing of the aorta, which involves the origin of the left subclavian artery.

Laboratory examinations add valuable information. Circulation times¹³ to the throat and upper extremities are within or near normal limits, while there is usually prolongation of the circulation time to the feet and perineum. Accurate measurements of the radial and femoral pulsations reveal a retardation of the femoral wave behind the radial wave of from 0.1 to 0.15 seconds.

Roentgen examination often shows the presence of notching of the lower border of some of the ribs. This is usually not present in childhood and is more likely to be found in adults. In addition, careful examination reveals a dilated ascending aorta with a small or absent aortic knob. In the oblique views, abnormal clearness can be seen in the region of the descending aorta. There is hypertrophy of the left ventricle. Direct visualization of the constricted segment may be demonstrated by angiocardiology.⁵ If radioopaque material is injected into the brachial vein, and serial roentgenograms are taken immediately afterward, the dilated ascending aorta, the constricted segment, and frequently the dilated mammary arteries may be seen. (Fig. 4.)

Electrocardiographic findings are of little value. Left ventricular preponderance is usually demonstrated. Abnormal T waves are sometimes seen and indicate myocardial damage with a poor prognosis.

2. Infantile type: In contrast to the paucity of symptoms during the first weeks or months in the adult type of coarctation of the aorta, children with the infantile type usually present very grave manifestations during this period. If the coarctation is complete or almost complete, the child is usually cyanotic and dyspneic at birth, dying very shortly thereafter. If the constriction is not so severe, the child will appear normal to casual examination, but after a few weeks or months, dyspnea, ashen-gray cyanosis, and often edema of the extremities will develop. Cardiac dilatation occurs, and frequently a precordial systolic murmur is heard for the first time. Blood pressure readings reveal hypertension of the upper extremities, usually higher in the right arm than the left,

with hypotension of the lower extremities. Femoral pulsations are usually present if there is a large patent ductus arteriosus. We have not been able to obtain satisfactory blood studies in a case of the infantile type, but from the anatomy the oxygen saturation of the blood in the upper extremities should be much higher than that in the lower extremities, due to the fact that blood in the upper extremities is from the left ventricle and ascending aorta while the blood in the lower extremities is a mixture of blood from this same source plus blood from the right ventricle and pulmonary artery shunted through the patent ductus arteriosus.

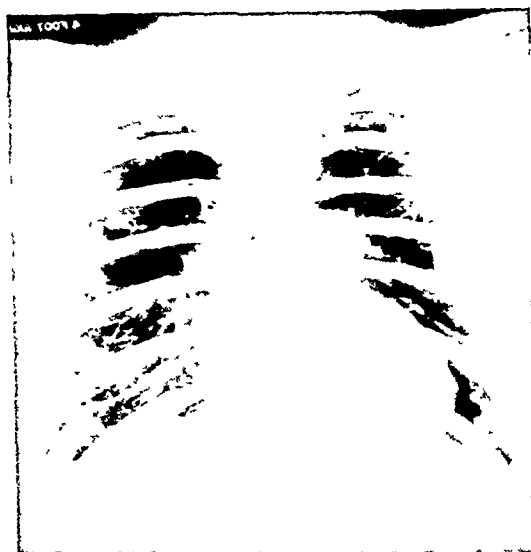


Fig. 4.—Coarctation of the aorta.

Surgical Treatment of Coarctation of the Aorta.—Coarctation of the aorta of the adult type is now a readily curable lesion. The operation for its correction consists of a transthoracic resection of the constricted segment of the aorta with an end-to-end anastomosis of the aortic ends. This procedure, first successfully done by Crafoord¹⁴ of Sweden and within a short time quite independently by Gross^{11b} of this country, is not so formidable as might be imagined. The extensive collateral system developed by patients with the adult type makes it safe to clamp the aorta for a period sufficient to resect and suture it. An occasional situation may be encountered in which it will be necessary to do a shunt procedure using the left subclavian artery as originally suggested by Blalock.¹⁵ The mortality should be no more than 10 or 15 per cent in good hands.

Since the incidence of degenerative cardiovascular complications and cerebral accidents is high in this group and since the life expectancy of the group as a whole is significantly reduced, it is our feeling that the operation is indicated whenever a significant degree of coarctation is present.

No successful operation on the infantile type has been reported. It is our belief, however, that an occasional patient may ultimately be successfully operated upon.

PULMONARY STENOSIS

Pathologic Anatomy.—Clinical differentiation of the various types of cyanotic congenital heart disease assumes greater importance with the more widespread application of great vessel surgery. This group is composed of several different types of abnormalities, the most frequent and most important of which is the tetralogy of Fallot, characterized by pulmonic stenosis or atresia, dextroposition of the aorta, interventricular septal defect, and right ventricular hypertrophy. Frequently there may be an associated deformed and narrowed conus or bicuspid pulmonary valve.

Cyanosis, which is one of the most striking features, is due to excessive amounts of reduced hemoglobin. The two most important causes for the unsaturation of arterial hemoglobin are decreased pulmonary blood flow and direct shunting of venous blood from the right ventricle into the aorta. Obviously, the greater the pulmonic stenosis and the greater the venous-arterial shunt, the more severe the cyanosis will be. *Polycythemia* and *general enlargement* of the capillary beds also contribute to the cyanosis. Despite the predominant venous-arterial intracardiac shunt, some blood is usually shunted from the left ventricle to the right. This has been shown by Bing and his co-workers,¹⁶ who demonstrated in the majority of their patients a higher oxygen content of blood in the right ventricle than that of the right auricle. Clinically, it is easy to demonstrate deepening of the cyanosis with exercise. In the laboratory¹⁶ following exercise, the arterial blood oxygen saturation drops sharply and the carbon dioxide content rises, in contrast to the findings of a normal person. As this same drop in oxygen saturation is seen in some patients with pulmonic stenosis following the Blalock-Taussig operation as well as in patients with the Eisenmenger syndrome (who have normal pulmonary blood flow), it must be due to an increased venous-arterial shunt. Following exercise, most patients with pulmonic stenosis show a significant fall in the ratio of oxygen consumed per liter of ventilation and a decline in the carbon dioxide produced per liter of ventilation. This is opposite to the increase in the oxygen and carbon dioxide ratios found with exercise in normal persons, and results from limitation of effective pulmonary blood flow due to the pulmonic stenosis, which prevents an increase in the oxygen consumption and carbon dioxide production proportionate to the increased volume of respiration.

Diagnosis.—Cyanosis may be present at birth, or it may appear later. Often, it will be absent during the first weeks of life and then appear at more frequent intervals until it becomes permanent. This delay may be due in part to slow closure of a patent ductus arteriosus, which increases the effective pulmonary blood flow as long as patency remains. Clubbing of the fingers and toes develops later and results from the low capillary oxygen tension. Dyspnea varies with the degree of oxygen unsaturation. Sudden attacks of dyspnea are occasionally seen, apparently due to a sudden increase in the volume of the intracardiac shunt. *Polycythemia* develops as compensation for the oxygen unsaturation and usually is roughly proportional to it. Frequently there is stunting of growth and malnutrition.

Examination of the heart usually reveals little or no cardiac enlargement unless cardiac failure is present. A systolic murmur is usually present, frequently accompanied by a thrill, with maximum intensity usually in the pulmonic area but occasionally maximal over the third or fourth interspace just to the left of the sternum. Approximately 5 per cent of patients have no detectable murmur. A split second sound over the base of the heart is not heard as this would be indicative of good functional closure of both pulmonic and aortic valves. The pulmonic second sound is usually soft or absent, although it is occasionally accentuated. (Figs. 5, A and 5, B.)

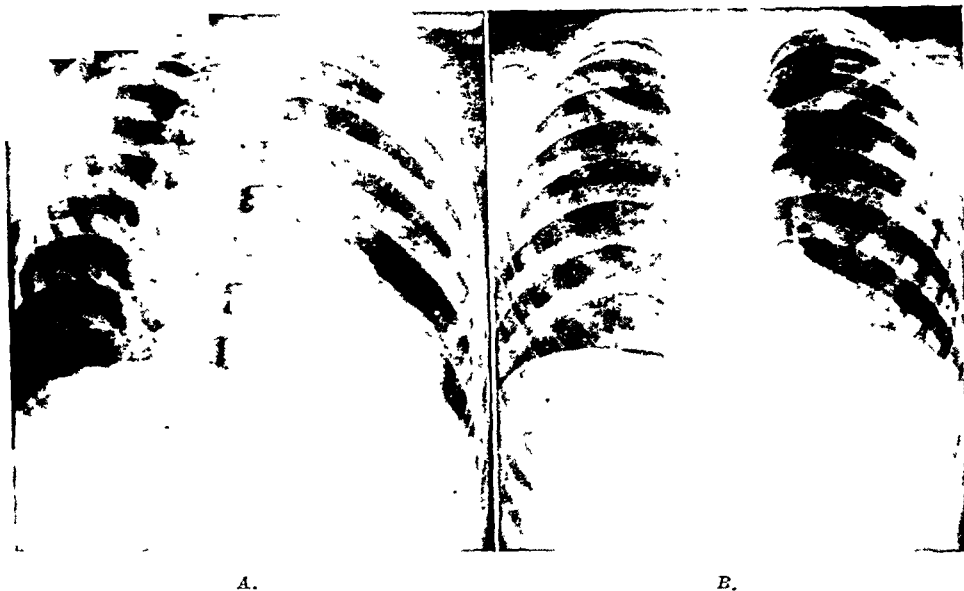


Fig 5—Tetralogy of Fallot, 4, right anterior oblique.

Roentgen examination of the heart in very small infants is frequently of doubtful value. In older infants and children typical diagnostic features can usually be observed as follows:

1. There is no general cardiac enlargement, although hypertrophy of the right ventricle is constant. In consequence, the heart appears enlarged to the left with the apex blunted and lifted off the diaphragm.

2. The normal prominence of the pulmonary conus is absent, frequently resulting in an actual concavity in this region. This is best visualized in the anteroposterior or right anterior oblique positions.

3. There is no pulmonary congestion, and pulsation of the pulmonary arteries is not visible. In the left anterior oblique position the region of the pulmonary artery is abnormally clear.

4. A barium swallow will reveal the location of the aortic arch. With a left-sided arch a concavity will be shown in the left side of the stream of barium, while the opposite is true with a right-sided arch. In the right anterior oblique view, enlargement of the right auricle and ventricle may be visualized

5. Angiocardiography will provide conclusive direct visual evidence. The aorta and the pulmonary artery are simultaneously visualized unless the pulmonary artery is too small to be identified. Enlargement of the right auricle and ventricle is seen, and shunting of the radiopaque material into the left ventricle may or may not be seen.

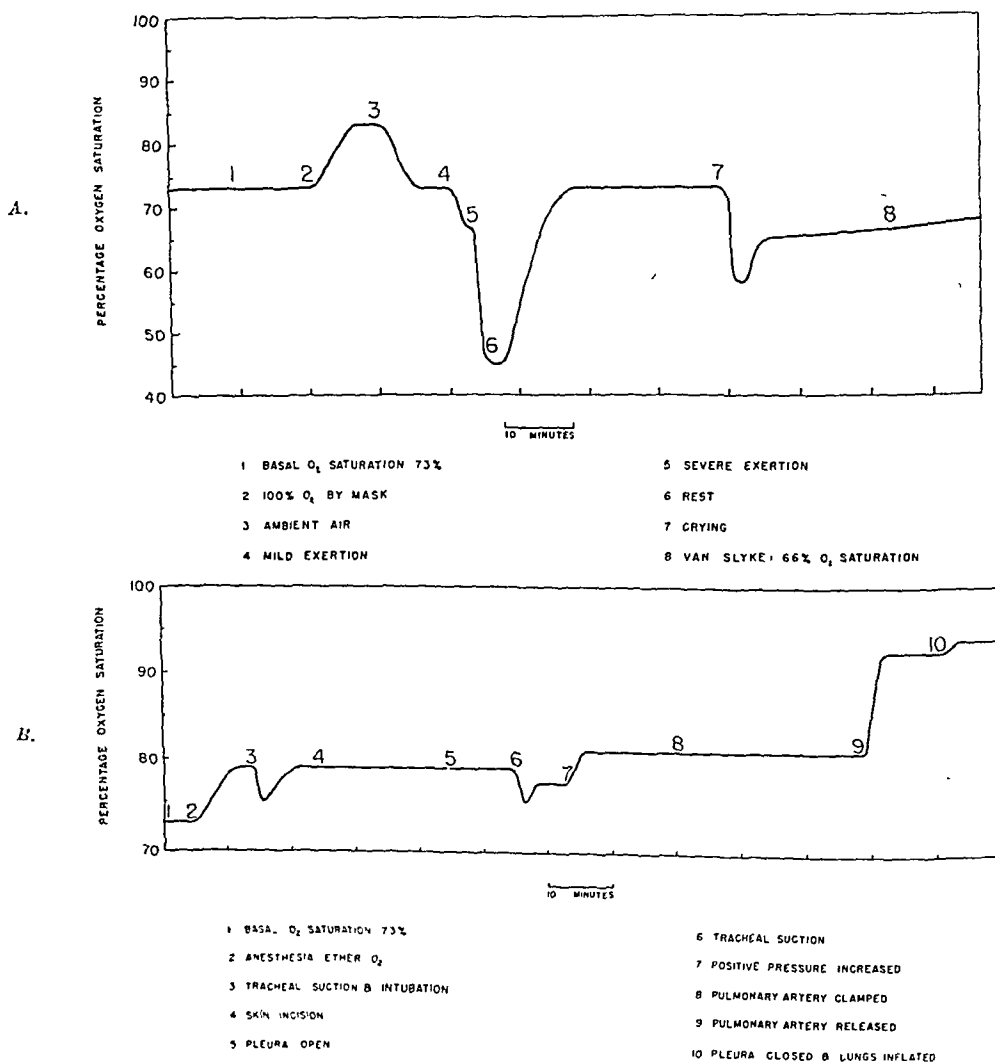


Fig. 6.—Tetralogy of Fallot: A, preoperative oximeter studies; B, operative and postoperative oximeter studies; C, postoperative oximeter studies. (For C, see opposite page.)

The electrocardiogram reveals right axis deviation, often with accentuation of the P waves. Conduction effects may occur due to the ventricular septal defect.

Catheterization of the heart chambers will provide additional valuable data. In cases where the pulmonary artery can be directly catheterized, the blood pressure can be shown to be much less than in the right ventricle. Bing and his co-workers¹⁶ have been able to calculate the percentage of total mixed venous blood reaching the lungs, thus showing the degree of pulmonic stenosis. Of much diagnostic value in pulmonary stenosis is the fall in the ratio of oxygen consumed per liter of ventilation together with a similar fall in the carbon dioxide produced following exercise. Circulation times from arm to tongue and arm to lung will be the same, showing that right ventricular blood flows simultaneously into the pulmonary artery and aorta. When fluorescein is used, a double end point is seen. The first is quickly seen when the dye passes from the right ventricle to the aorta and then to the lips. The second end point is delayed, with a portion of the dye first going through the pulmonary vessels, to the left auricle and ventricle, and finally to the aorta and lips.

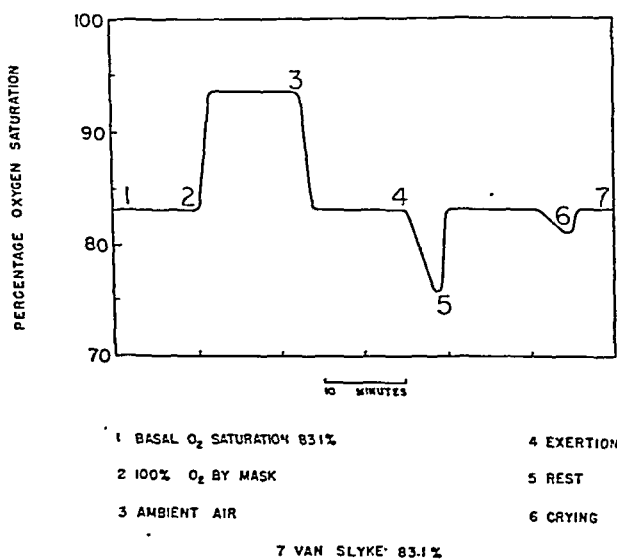


Fig. 6, C.—(For legend, see opposite page.)

Studies on patients with pulmonary stenosis by means of the Millikan-Smaller recording oximeter are being done by us and are proving to be of value both diagnostically and prognostically. The oximeter is a recently developed electronic device which records by photoelectric colorimetry the color changes of the intact, fully flushed ear lobe. Oxyhemoglobin transmits more red light than does reduced hemoglobin. By means of a lamp on one surface of the ear lobe, a light-sensitive cell on the other side, and a red color filter between, the change in transmission of oxygen can be measured and interpreted in per cent saturation of hemoglobin with oxygen. The warmth from the lamp on the ear lobe causes a maximum vasodilatation, and, therefore, the mixed blood in the optical pathway approaches very accurately the composition of

arterial blood. This device is now sensitive enough so that changes in the arterial oxygen saturation are recorded within 0.45 of a second.

Pulmonic stenosis cases are proving to have a very characteristic oximeter pattern. This pattern consists of a prolonged saturation time (saturation is that period required for blood to equilibrate maximally with the alveolar oxygen when 100 per cent oxygen is inspired) and a rapid severe hypoxia with exertion. (Figs. 6, A, 6, B, and 6, C.)

The oximeter during operations for arterial shunt has shown a magnificent response in immediate elevation of saturation values as soon as the shunt has been completed and the clamp removed. Postoperative oximetric studies on patients with pulmonic stenosis have shown the almost immediate return to a normal pattern—that is, a drop in saturation time to a normal of two or three minutes and a much less severe hypoxia on exertion. We are beginning to feel that the oximeter has a valuable place in the diagnosis of cardiovascular congenital defects.

Oximetric studies have been of unusual interest in the so-called Eisenmenger group since in several cases proved by operation to fall into this poorly understood category, a consistent type of oximeter pattern has been obtained. (Fig. 7.) This is characterized by a less marked fall in the oxygen saturation following exercise than is seen in cases of pulmonic stenosis. The drop is usually not over 10 per cent with a low level usually not below 50 per cent. Deep, slow respirations result in a serrated type of curve with the increasing component occurring during inspiration and the decrease with expiration. This particular pattern has not been seen in normal individuals or in patients with pulmonic stenosis either pre- or postoperatively.

Differential Diagnosis of Pulmonic Stenosis.—As the main objective for surgical treatment is to increase the pulmonary blood flow, it is necessary to pick out and eliminate from operative consideration those children who are cyanotic and yet have a normal pulmonary blood flow, as they will not benefit from operation. In the first few weeks or months of life, most of the children with very severe and complicated cardiac defects will die. In children beyond this age group, the majority with cyanotic heart disease are examples of the tetralogy of Fallot. Of the remaining minority, there are several important groups.

The Eisenmenger complex: This consists of an interventricular septal defect with overriding of the aorta, dilated pulmonary artery, and usually hypertrophy of the right side of the heart. Usually less venous blood is shunted into the aorta than in the tetralogy of Fallot, so that cyanosis is usually later in onset and is less intense. Following exercise there is less drop in the arterial oxygen saturation, and there is an increase in the ratio of oxygen consumed and carbon dioxide produced per liter of ventilation. The patient usually shows a more normal physical development. Results of physical examination of the heart are similar to those found in the tetralogy of Fallot except that the pulmonic second sound is usually clear and loud, and a diastolic murmur may occa-

sionally be heard in the pulmonic area. Roentgen examination reveals an exaggerated pulmonary conus with pulmonary congestion and often pulsation of the hilar vessels. The electrocardiogram is similar to that seen in the tetralogy of Fallot. Angiocardiography will demonstrate the presence of the overriding aorta and large pulmonary artery. Direct catheterization of the heart will furnish data by which the adequacy of the pulmonary blood flow can be calculated. (Fig. 8.)

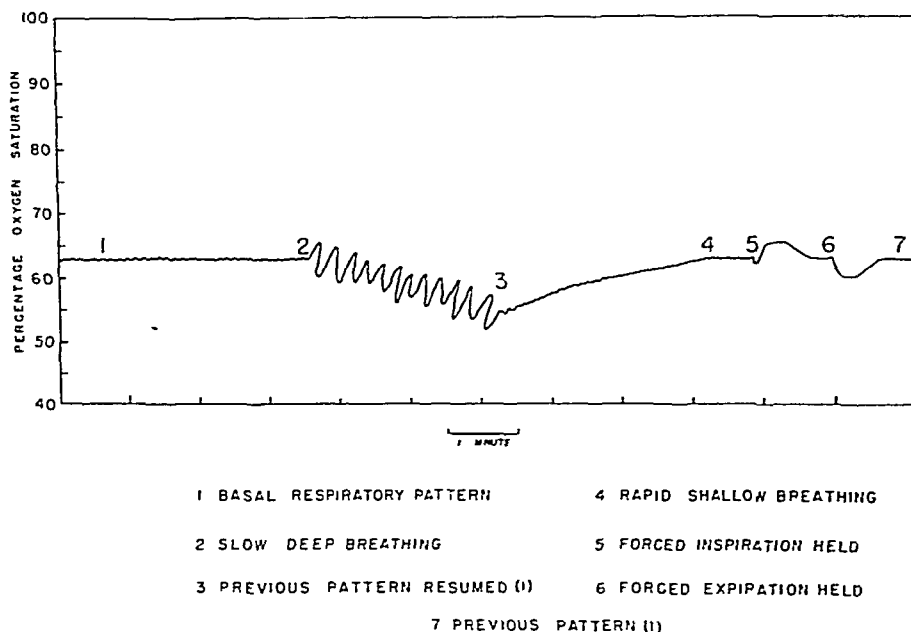


Fig 7—Eisenmenger's syndrome, oximeter studies

Persistent truncus arteriosus: In this condition a single great vessel arises directly from both ventricles, above a defect at the base of the interventricular septum. The blood supply to the lungs may be derived through pulmonary arteries which branch off the common vessel or through smaller bronchial arteries with no trace of the pulmonary arteries. In the former case cyanosis may be minimal or absent while in the latter case cyanosis is always present and may be very severe. Most children with persistent truncus arteriosus die very early, but rarely the lesion is encountered in later childhood or adult life.

Examination usually reveals a loud systolic murmur over the precordium with an accompanying thrill. The pulmonic second sound is loud and pure. Roentgen examination¹⁷ reveals a sharp angulation of the cardiac shadow to the left of the sternum. The pulmonary conus is missing, and the aortic knob is prominent. In the left anterior oblique view, the right ventricle is very large and extends out from the aorta toward the chest wall like a shelf. Angiocardiography should easily show the persistence of the single great vessel. The

electrocardiogram may show accentuation of the P waves or slight right axis deviation. (Figs. 9, A and 9, B.)

Complete transposition of the great vessels: Complete transposition with no other compensating cardiac lesion always results in very early death in the neonatal period. Some patients who have compensating defects, however, live to childhood or even early adult life. Auricular or ventricular septal defects or patent ductus arteriosus are the most common accompanying abnormalities



Fig. 8.—Eisenmenger's syndrome.

Cyanosis is severe and present from birth. The heart enlarges rapidly, presenting a globular shape on roentgenoscopic examination, with more enlargement of the right side than the left. The aorta lies anterior to the pulmonary artery, so that the great vessel shadows may be narrowed in the anteroposterior view and widened in the lateral view. Angiocardiography should be of great value here.

Complete septal defects: There may be absence of either the interauricular or interventricular septum, or both. Interauricular septal defects are usually not accompanied by cyanosis except terminally. Interventricular septal defects are usually accompanied by moderate cyanosis unless complicated by an accompanying pulmonic stenosis. Most individuals with such septal defects die quite early, although some live to childhood or early adult life. The heart is quite large, particularly the right ventricle. The electrocardiogram reveals a large biphasic QRS complex in all leads.

Stenosis or atresia of the tricuspid valve is usually associated with a hypoplastic right ventricle and usually an interauricular and interventricular septal defect. Cyanosis is persistent and usually present at birth. Roentgen examination reveals enlargement of both auricles and the left ventricle with a small right ventricle. Left axis deviation is seen in the electrocardiogram.

Treatment of Pulmonic Stenosis.—The surgical treatment of pulmonic stenosis represents one of the most fascinating and brilliant accomplishments in surgery. The work of Blalock and Taussig on this problem is too well known to warrant review here. Suffice it to say that credit for a large part of the recent development in the surgery of congenital cardiovascular defects stems directly from their work.

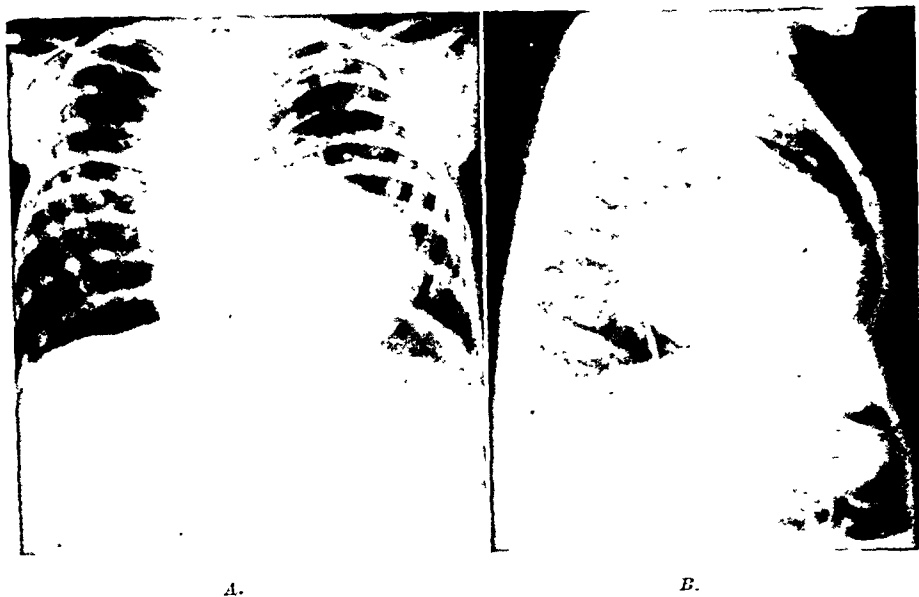


Fig. 9.—A, Persistent truncus arteriosus with right-sided arch. B, Persistent truncus arteriosus with right-sided arch; right anterior oblique.

As pointed out previously, the essential defect in this group of anomalies is the pulmonic stenosis with the subsequent inability of the heart to propel a sufficient volume of blood to the lungs for normal oxygenation. Blalock's operative procedure consists in providing an arterial shunt to by-pass the pulmonic obstruction. This is accomplished by anastomosing the distal end of one of the large systemic vessels arising from the aortic arch to the side of either the right or left pulmonary artery. In the typical case—that is, pulmonary stenosis complicated by the other defects making up the true tetralogy of Fallot with a right aortic arch—the most generally used procedure is a left thoracotomy with utilization of the subclavian artery arising from the innominate.

However, a very wide variety of arterial anomalies may be encountered, and it is frequently necessary to improvise according to the anatomy that presents itself. It has been found, for instance, that in children one can sacrifice the carotid without producing recognizable central nervous system manifestations. Potts, Smith, and Gibson¹⁸ have recently proposed a very useful modification in which they do a direct anastomosis between the aorta and the pulmonary artery. This is accomplished by the use of an ingenious clamp which permits a sufficient flow of blood through the aorta during the time the anastomosis is being carried out.

While our experience with these procedures is limited when compared to the extensive experience of Blalock, we have come to decide that both types of operative procedures are useful and applicable. In patients with a right aortic arch, we are now doing the Blalock type of operation on the left side, using the subclavian artery, which in these cases arises from the innominate. In those cases of pulmonic stenosis in which the arch and aorta present and descend on the left side, we prefer the Potts-Smith type of procedure, doing a side-to-side anastomosis between the aorta and the left pulmonary artery.

With either type of procedure, the mortality is steadily declining as experience is gained. We have had no deaths and no postoperative complications in our last ten cases. Our results, like those of Blalock, have been the poorest in the older age group. Like him, we feel that it is better to wait if possible until the patients are 2 years of age. However, if the status of the patient indicates that he will not survive without the operation, the procedure is done irrespective of age, and some of the most dramatic results have been achieved in the young group who are seriously handicapped.

ANOMALIES OF THE AORTIC ARCH

Clinical recognition of various types of developmental abnormalities of the aortic arch and associated great vessels has been most difficult in the past but is becoming easier due to improving methods of roentgen visualization. The types of anomalies which may be associated with clinical symptoms are:

1. Right-sided aortic arch.
2. Double aortic arch.
3. Anomalous right subclavian artery.
4. Anomalous left subclavian artery.

Right-sided Aortic Arch.—According to Congdon,¹⁹ the main blood vessels cephalad to the heart consist of an arterial trunk from which arise a series of six branchial arteries, connecting paired ventral and dorsal aortas. The first and second arches disappear early. The ventral aortas with the third arches persist as the external carotids, and the cephalad portions of the dorsal aortas persist as the internal carotids. The fourth arch usually persists on the left side as the aorta while the fourth right becomes the innominate artery with disappearance of the dorsal aorta between the right subclavian and the point of fusion of the two dorsal aortas. The fifth arches disappear, and the sixth arches form the pulmonary arteries and patent ductus on the left. (Figs. 10, A and 10, B.)

Persistence of the right-sided fourth arch with disappearance of the left one results in a right-sided aortic arch. This crosses to the left behind the esophagus, usually at the level of the bifurcation of the trachea, although it may occasionally descend lower on the right of the esophagus before crossing. It crosses above the right main bronchus, and the right recurrent laryngeal nerve passes around the arch instead of the right subclavian artery. Persistence of the distal portion of the sixth left arch as the ductus arteriosus or ligamentum arteriosum will combine with the right-sided aortic arch to produce a ring around the trachea and esophagus which may produce symptoms.

If both of the fourth arches persist, a double aortic arch will result. Both arches may be patent, or one may be only partially patent, the remainder of its length being represented by a fibrous cord. In such cases, the trachea and esophagus are encircled. The left arch is almost always smaller²⁰ than the right, although occasionally the reverse has been found. Schall and Johnson²¹ report a case with both arches of equal size. In two cases reported by Sweet and his co-workers,²² innominate arteries were present due to persistence of portions of the dorsal aortae.

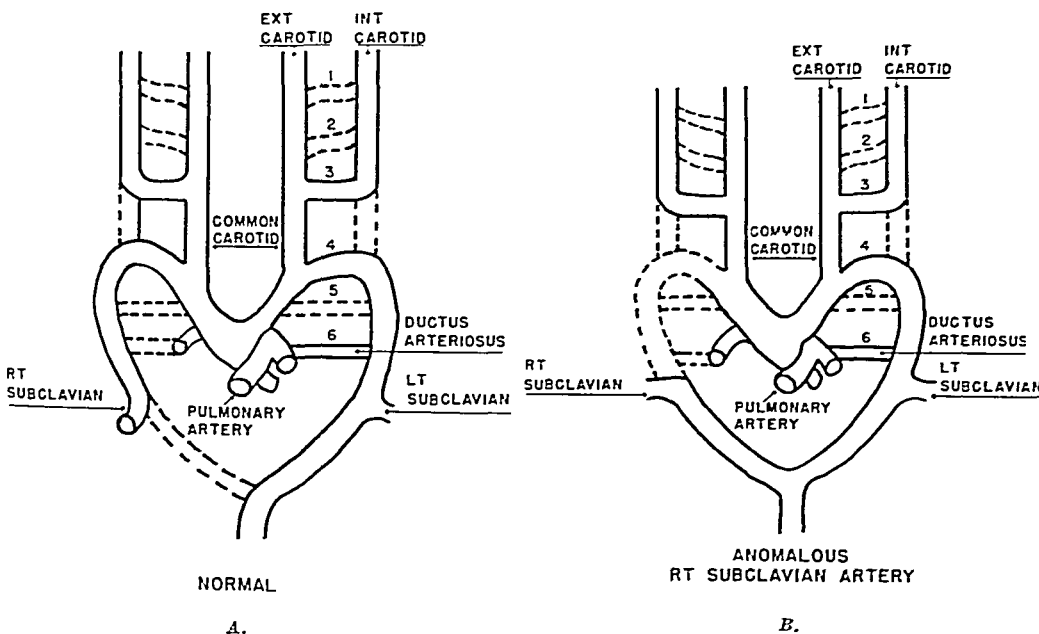


Fig. 10.—Development of great vessels. A, normal; B, anomalous right subclavian artery.

Anomalous right subclavian artery is seen with a left aortic arch as described by Goldbloom.²³ The right subclavian normally arises from the seventh intersegmental artery, arising at the point of fusion of the dorsal aortas. With the growth and ascent of the right subclavian up the right branchial arch, that portion of the arch which extended caudad to the point of fusion atrophies and disappears. In the development of the anomalous right subclavian artery, the cephalic portion of the right fourth arch between the right subclavian and right common carotid arteries atrophies while the portion of the fourth arch caudad to the right subclavian continues to grow. As the result, the right subclavian arises from the left aortic arch, crossing to the right side behind the esophagus. An anomalous left subclavian artery may be formed in a similar manner with a right-sided aortic arch.

Symptoms and Diagnosis.—Any of the anomalies of the aortic arch may be present and cause few, if any, symptoms. When a double aortic arch or a right-sided aortic arch with persistent ductus arteriosus or ligamentum arteriosum is present, the symptoms are due to direct pressure on the esophagus and

trachea. Respiratory stridor and dysphagia are most common. During early infancy the former is usually most prominent while the infant is on a liquid diet. With the introduction of solid foods, the latter usually makes its appearance. Stridor is usually mainly inspiratory, is worse with excitement and while feeding, and may be severe enough to cause retraction and cyanosis. It tends to lessen or disappear during sleep.²⁴ Feedings are often taken slowly and with much difficulty, especially solid foods. Vomiting is frequent and immediately follows the feeding.



A.

B.

Fig 11—A, Right-sided aortic arch. B, Right-sided aortic arch; right anterior oblique view with barium swallow

In individuals with anomalous subclavian arteries or right-sided aortic arch, dysphagia and vomiting may be the most prominent symptoms. With dilatation of the right-sided arch, pressure on the trachea, right main bronchus, and recurrent laryngeal nerve may result in dyspnea, cough, wheezing, and laryngeal paralysis. Inequality in the radial pulses, trophic changes in the upper extremities, and pressure on the thoracic duct have been described with anomalous subclavian arteries.²⁵

Röntgen findings will vary depending on the type of anomaly.

1. *Right-sided aortic arch*: The aortic shadow is seen to the right of the sternum and not in its usual place on the left. In the right anterior oblique view the ascending and descending portions of the aorta are separated, as is normally seen in the left oblique view. With barium in the esophagus, an anteroposterior view will show a concavity in the right side of the esophagus at the level of the aortic arch, and on oblique view the esophagus is seen displaced forward by the aorta which passes behind. This filling defect pulsates strongly. Arteriography shows the exact location of the aortic arch. (Figs. 11, A and 11, B.)

*A.**B.**C.*

Fig. 12.—*A*, Double aortic arch; anteroposterior view. *B*, Right anterior oblique. *C*, Left anterior oblique.

... symptoms are ... is split ... The ... In case of ... The ... either of the ... gives immediate ... and permanent relief from the symptoms.

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2. *Double aortic arch*: Roentgen examination will usually show a picture compatible with a right aortic arch with indentations of the esophagus posteriorly and on both the right and left sides. The opaque material usually shows more of a filling defect than with an uncomplicated right aortic arch. Bronchograms will show tracheal compression. (Figs. 12, A, 12, B, and 12, C.)

3. *Anomalous subclavian arteries*: The characteristic picture is of a pulsating indentation in the posterior wall of the barium-filled esophagus. This is below the level of the aortic arch and is not accompanied by lateral displacement of the esophagus, except for that due to the aortic arch, which is higher. Accompanying erosion of the adjacent vertebral body may be demonstrated.

Anomalies of the aortic arch may go undiscovered throughout the patient's life because they frequently do not give rise to signs or symptoms. On the other hand, they may cause impingement on either the trachea or the esophagus and cause marked symptoms due to obstruction of these structures very early in life.

The two types of deformity that most commonly give rise to symptoms are (1) the so-called aortic ring in which, as explained previously, there is a split aorta with left and right components, and (2) aberrant subclavian arteries which pass either in front of or behind the esophagus and/or trachea. The symptoms resulting from these anomalies have been described. Their surgical correction consists in ligating and dividing the offending vessel. In cases of aortic ring compression of either trachea or esophagus, it is important to resect that part of the ring which does not give rise to important branches. These procedures are easily accomplished through an upper thoracotomy either of the posterolateral or anterior type. Section of the offending vessel gives immediate and permanent relief from the symptoms.

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AN EVALUATION OF THE PENICILLIN TREATMENT IN EARLY CONGENITAL SYPHILIS

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DURING the brief period in which penicillin has been recognized as an effective treatment for syphilis, the demands for information on its ultimate results have been overwhelming. It is, of course, needless to say that even at this date penicillin therapy is too new and the findings on it still too limited to permit any accurate determination of the final efficacy of the drug. Particularly is this true in the field of congenital syphilis. Therefore, I shall attempt here only to evaluate, on the basis of extant information in conjunction with my own experience, what would seem to constitute a current preferred penicillin treatment for syphilitic infants and children.

Unfortunately, the published reports on the use of penicillin in congenital syphilis are confined mainly to cases of acquired infantile and early congenital syphilis. This apparent limitation of findings may be attributed to several obvious causes, among them (1) the comparatively small number of previously untreated cases which have appeared in any one institution; (2) the difficulty of obtaining penicillin in the first period of its use; (3) the apparent impossibility of adequate follow-ups; (4) the shortness of time required to determine response to treatment of early congenital syphilis.

The available accounts describe such differing potencies of penicillin given in so small a series of insufficiently followed cases, that any evaluation of efficacy, optimum dosage, and correct period of administration must necessarily be subject to modification as research progresses.

Early records tell of the use of the crude form of the drug with dosage based mainly on infant weight, comparable to dosage based on weight in adults. The period of administration was generally for seven or eight days. More recent investigations teach us that these early dosages were much too meager and indicate the necessity of larger dosage over a longer period of time, with repeated courses required in some instances. Experience has also shown that the early refinement of penicillin reduced, rather than improved, its potency in either adult or congenital syphilis. Sodium penicillin (G) in aqueous solution is now found to be the most potent form of the drug for treating syphilis.

However, before we proceed to appraise in detail the outstanding published information on early congenital syphilis, which constantly comes to pediatric attention, and in order to establish the effects of penicillin on the various manifestations of the disease, it would seem wise to review here some of the criteria for diagnosis.

Read before the Pediatrics Section of the New York Academy of Medicine.

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Of primary diagnostic importance are quantitative serologic tests on the blood of newborn syphilitic infants. Sufficient reagin may be passed over from the mother's blood through the placenta to give a positive serologic reaction in the cord blood or in the infant's blood. Conversely, but much less frequently, a negative reaction in the cord blood may be found in a child in whom syphilis later becomes apparent. Further quantitative tests should be done at least once a week for six to eight weeks. In the nonsyphilitic infant the titer decreases rapidly to normal within a period of about six weeks, while in the syphilitic infant it rises steadily—except in cases where the infection was acquired late in pregnancy, in which event the titer may fall at first only to rise later. If the serologic test is positive at the end of six or eight weeks, one should assume the child to be syphilitic even without other evidence of syphilis.

However, corroborative evidence of early syphilis is usually present and manifested by: (1) mucocutaneous lesions, or a chancre from which a positive dark field may be obtained; (2) roentgenographic signs of bone syphilis, appearing in about 70 to 80 per cent of infants under 3 months of age (older children are less likely to show bone changes); (3) snuffles, anemia, enlarged liver and spleen, adenopathy, pseudoparalysis, gastrointestinal disturbances, and changes in the spinal fluid in a certain per cent of cases. These positive spinal fluid changes occur most frequently in younger infants.

In the reports which follow in chronological order, diagnoses of early congenital syphilis were made on the serologic as well as on the clinical findings. The results were based on the response of these manifestations to penicillin therapy.

Before proposing a schedule for combating the disease with penicillin, let us review the findings of other workers in this field.

DIGEST OF REPORTS

*I.—Platou*¹ in 1944 published a report of the results of penicillin treatment in sixty-nine cases of early congenital syphilis pooled from clinics in five cities. Thirty-nine of these patients were followed from four to twelve months. In all cases a total dosage of 16,000 to 32,000 Oxford units per kilogram of body weight were administered in sixty injections over a 7½-day period.

Results:

	No. Cases
Clinical results	
Course uneventful	37
Clinical relapse	2
Serologic results	
Negative	21 or 54 per cent
Reversed to doubtful	4 or 10 per cent
Positive—titer decline	9 or 23 per cent
Serologic relapse	5 or 13 per cent

Treatment reactions in 53 per cent of the cases were within twenty-four to forty-eight hours after beginning treatment. Reactions consisted of mild elevations of temperature which lasted no longer than three days.

There were three deaths in debilitated infants during treatment. These deaths were attributed to the general debilitated state rather than to penicillin.

Conclusions from the Platon 1944 study: The total dosage must probably be at least 40,000 units per kilogram of body weight in early congenital syphilis. The importance of adequate pediatric care in the acutely ill babies is stressed.

II.—Ingraham² in March, 1946, published a résumé of his results in treating early congenital syphilis in twenty-six infants whose average age was 3.6 months. All patients had clinical evidence of the disease with, in many cases, positive dark-field examination of the cutaneous lesions. Almost all had roentgenographic evidence of bone changes. Sodium penicillin was used in dosages of 10,000 to 74,000 units total per pound of body weight. The children were observed over a period of from 7.6 to fifteen months.

Results:

80 per cent fall in titer—average eighty eight days.

50 per cent seronegative—average 168 days. One child had a total of 74,000 units per pound in fifteen days, became seronegative in seventy-eight days.

50 per cent of patients treated with 16,000 units per pound of body weight became seronegative within sixteen months, while 85.7 per cent of patients receiving larger doses became seronegative in six months.

Death—Five or 20 per cent, due to general debility or intercurrent infection.

Treatment reactions in 40 per cent, consisting of severe gastrointestinal disturbances and temperature reactions within the first forty eight to seventy two hours after treatment was begun. These reactions had a tendency to regress as treatment was completed.

Conclusions from Ingraham study: It is necessary to use a total dosage of 20,000 units or more per pound of body weight. Treatment should be extended from ten to fifteen days

III.—Nielsen and his associates³ in June, 1946, reported on the treatment of twenty-eight previously untreated cases of early syphilis in the Midwestern Medical Center at St. Louis. Of the cases observed over a period of from two to sixteen months, seven were acquired and twenty-one congenital. In all the acquired cases there were positive dark-field examinations. The total range of dosage was from 80,000 to 300,000 units per kilogram of body weight (figure includes retreatment). The majority of patients received 100,000 to 125,000 units per kilogram.

Results:

25 per cent free from syphilis (clinically and serologically).

21.3 per cent with titer less than 4 Kahn units.

35.7 per cent strongly positive serology (nine cases with declining titers).

14 per cent lost from observation

One patient died on the eighth day; had jaundice and was debilitated on admission.

Disappearance of spirochetes from lesions in four to forty eight hours

Rapid and complete healing of lesions. Clearance of snuffles following disappearance of cutaneous and mucous membrane lesions.

In three patients with periostitis, clinical disappearance in one month and, according to roentgenographic studies, complete healing in three months.

Hersheimer reaction in nine cases

Definite improvement in children's nutritional state both during and after penicillin therapy.

Noninterference of therapy with the intake or retention of food in infants

Existence of spinal fluid changes in two cases (In one case where post treatment examination of spinal fluid was made, there was a decline of from 20 to 4 Kahn units. The colloidal gold curve, total protein level, and cell count both before and after treatment were normal)

Conclusions: In Neilsen's patients, who received larger doses of penicillin, the results just listed were obtained

Report 4.

*IV.—Platon*⁴ in January, 1947, reported on the treatment of 252 cases of early congenital syphilis that were treated in five university clinics in different parts of the United States. Unfortunately, in this report, as in others, there was a great variation in dosages in the individual groups varying from 12,000 to 150,000 units per kilogram of body weight. Dosages less than 40,000 units per kilogram of body weight were given in sixty injections over a 7½-day period and dosages over 40,000 units per kilogram of body weight were given in 120 doses over a fifteen day period

Results:

74 per cent satisfactory in infants receiving up to 39,000 units per kilogram of body weight.

89.3 per cent satisfactory in infants receiving more than 40,000 units per kilogram of body weight.

10.7 per cent deaths. These occurred as frequently in the mild as in the severe form of the disease and were attributed to causes secondary to syphilis rather than to treatment. Nineteen of the twenty five deaths occurred in infants under 3 months of age

72 per cent spinal fluid abnormalities (in ninety one infants tested) before treatment, and 20.9 per cent abnormal fluids six months after treatment.

50 per cent treatment reactions consisting of mild to moderate increase in temperature.

Ten infants had mild Hersheimer reactions. Treatment was not discontinued

Six clinical relapses occurred three to eleven months after treatment. All responded to a second course of treatment doubling the initial dosage.

Platon found that there was no significant difference in satisfactory results in the different age groups and that the longer patients were followed after treatment, the more satisfactory and fewer unsatisfactory results were obtained. Regardless of the amount of treatment, he thought that the nutritional status of the patient, when treatment was initiated, had some prognostic import although this was not borne out by the data.

Conclusions: Dosages of over 40,000 units of penicillin per kilogram of body weight, given over a fifteen-day period, are necessary.

*V.—Moon-Adams*⁵ in 1947 made a study of forty-eight cases of early congenital syphilis, adequately followed at Bellevue Hospital in New York City. The patients ranged from newborn infants to 3 years of age. In 88.8 per cent

there was clinical evidence of congenital syphilis. Total dosages of 9,500 units to 100,000 units per kilogram of body weight were administered over a period of from three to fifteen days.

Results: These are shown in Table I.

TABLE I

AGE	NO. CASES	% SATIS- FACTORY	% UNSATIS- FACTORY	DEATHS
0-3 months	26	85	3	12%
3-6 months	13	85	7.5	7.5%
6-12 months	2	50	--	50%
1-3 years	7	57	43	
All cases	48	81	10.5	8.3%

Conclusions: At least 100,000 units of sodium penicillin per kilogram of body weight, over a period of fifteen days in 120 divided doses, must be administered.

SUMMARY AND SUGGESTED PLAN FOR TREATMENT

From the information we have gained to date on the results of penicillin on early congenital syphilis, it is possible to formulate an effective treatment schedule for the disease. One must realize, however, that as penicillin therapy is subjected to further study and the drug itself to changes in type and potency, this schedule may require alterations.

On the basis of the study of the current literature, plus my own experience, it can now be agreed that a total dosage of over 20,000 Oxford units of sodium penicillin per pound of body weight is necessary to combat early syphilis in infants and children. Certainly, in those adequately followed patients who received larger doses the best results have been obtained.

A suggested plan for treatment would be: the administration of 50,000 Oxford units of the aqueous solution of sodium penicillin per pound of body weight at three-hour intervals over a period of fifteen days, totalling 120 doses. In debilitated infants, it would probably be advisable to reduce the initial dosage on the first day by about one half. When a febrile or Herxheimer reaction occurs, treatment may usually be continued. For those patients who show no reduction in serologic titer within six months after treatment, or in whom the serologic titer increases or clinical relapse occurs, a second course of treatment can be recommended. The repeated course should double the initial dosage. If this also has no beneficial effect on the serologic titer or clinical manifestations, then a third course combining even larger doses with fever therapy—age and general health permitting—will be necessary.

In administering the proposed treatment one may expect the following response of the serologic and clinical manifestations of early congenital syphilis:

Serologic Response.—The serologic reaction of the blood should become negative in from three months to one year and should begin to decrease in titer within a few months after treatment. The average period for a sero-negative reaction is between seven and eight months after the initiation of treatment. Positive serologic tests on the spinal fluid may be found in about

50 to 75 per cent of young infants and in only 20 to 30 per cent of older infants before treatment, demonstrating that there is a tendency to spontaneous reversal of the spinal fluid serology. The majority of these abnormal fluids will respond to penicillin treatment within six to eighteen months.

Clinical Response.—

1. Rapid healing of the mucocutaneous lesions, complete healing within two to three weeks.

2. Disappearance of the spirochetes from the positive dark-field lesions within twenty-four to seventy-two hours.

3. Disappearance of rhinitis and snuffles within two to eight weeks.

4. Disappearance of roentgenographic abnormalities within two to six months.

5. Disappearance of hepatic and splenic enlargements and adenopathy within three months.

Reactions.—Development of treatment reactions in about 40 to 50 per cent of the cases may be expected. These reactions are usually mild and consist mainly of a 1 to 3° F. rise in temperature which will disappear as treatment is continued. Some children will have gastrointestinal disturbances, and in a few instances a Herxheimer reaction will develop. In most instances reactions are no indication for discontinuing treatment.

One of the most important aspects of penicillin treatment, and a part that cannot be overemphasized, is the general pediatric care of syphilitic infants both during and after treatment.

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NEW CONCEPTS OF OSTEOMYELITIS IN THE NEWBORN INFANT

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THE majority of reported studies of osteomyelitis in the newborn infant emphasize that the disease runs a benign course. In spite of adequate use of penicillin and sulfa derivatives, this has not been our experience during the years these drugs have been in common use. On the contrary, in some cases we have found osteomyelitis in the newborn infant to be among the most severe and serious infections encountered.

In 1933 Dunham¹ reviewed the literature and uncovered only eight recorded cases of septicemia in the neonatal period. She reported an additional thirty-nine cases of septicemia due to various types of organisms. Four of the thirty-nine developed osteomyelitis. Subsequently Dillehunt² and Cass³ each reported several cases of osteomyelitis in newborn infants. In general these observers agreed that the child usually exhibited no severe systemic effects and stated that the prognosis for recovery was good. As late as 1942 Stone⁴ emphasized the benign course of osteomyelitis in the newborn infant. The collected case reports of these authors frequently record a presenting complaint of swelling about a joint and loss of appetite, without severe systemic disturbance. Rapid healing of osseous lesions without sequestration and with negligible deformity apparently was the rule, and Green⁵ felt there was sufficient difference in the course of the disease in infants to distinguish between cases in children under 2 years of age and those over 2 years of age. Green, alone, refers to the number of patients who succumbed to the disease.

Einstein and Colin⁶ in 1946 presented a number of roentgenograms of osteomyelitis in infants under 6 months of age. Some of their illustrations showed permanent deformities of the bones. Nevertheless, they stressed the benign course of the disease as contrasted with that in older children. Shulman⁷ reported a case of osteomyelitis with recovery in a 19-day-old infant. In the same year Greengard,⁸ in an excellent review of osteomyelitis in infants, pointed out that there were two types, a *benign form* without severe systemic reaction and a *severe form* which followed a stormy course and resulted in severe deformities. Our studies have led us to agree with these conclusions.

It was the observation of several unusual cases of osteomyelitis in the newborn infant which aroused our interest in the disease. The case of J. A. is reported in detail because it is the most unusual one.

CASE REPORTS

CASE 1.—A one-month-old male infant, J. A., was admitted with a history of diarrhea of two weeks' duration. The stools had been green and liquid, between twelve and fifteen movements a day at the onset with gradual subsidence to five or six a day just before admission. His appetite had been poor, and weight loss, irritability, restlessness, and fever were manifested.

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The child had been born spontaneously at full term, gravida iii, weighing 7 pounds and 4 ounces, after twelve hours of uncomplicated labor. The mother and baby went home at the end of seven days, and the baby was in good health except for mild infection of the buccal mucosa which the doctor told the mother was "thrush." On the third day after discharge from the hospital the patient began to have a diarrhea which formula changes did not correct.

The family history was not contributory. Father, mother, and two siblings were alive. There was no history of familial disease tendencies, and the parents' Wassermann reactions were negative.

Physical examination disclosed a rectal temperature of 100° F. in a 5 pound, 15 ounce, slightly cyanotic infant, with mottled extremities, sunken eyes, and evidence of dehydration. The fontanelles were depressed, and the mucous membranes were dry. Eyes, ears, nose, and throat were not abnormal. Heart and lungs failed to disclose any abnormalities. The liver could be felt 2 cm. below the costal margin, but the spleen was not palpated. The child had been circumcised, and there was no evidence of infection of the wound. His legs were swollen and he held them flexed on his abdomen. He cried when they were extended. Reflexes were equal and active, and no signs of pathologic change in the central nervous system were present.

Laboratory studies on admission revealed a hemoglobin of 10 Gm. with 19,550 leucocytes, 53 per cent polymorphonuclear cells, 30 per cent lymphocytes, 24 per cent monocytes, 2 per cent eosinophiles, and 1 per cent basophiles. Urine examination revealed a one plus albumin; otherwise there were no abnormal findings. The carbon dioxide combining power was 17 c.c. volumes per cent. A lumbar puncture revealed 4 leucocytes and 35 mg. per cent protein with 61 mg. per cent sugar and 626 mg. chlorides. Culture of the fluid was negative. Blood serology was negative.

Course: On admission the infant was treated as a diarrhea patient and intravenous fluids, plasma, and 10 per cent Amigen were started. Sulfadiazine, 7.5 c.c. intravenously, was given daily (0.42 Gm. in a 5 per cent solution). The rectal temperature remained within essentially normal limits until the fourth hospital day when it rose to 102° F. The patient's condition became worse and a blood transfusion was given. A blood culture taken on admission was reported growing hemolytic *Staphylococcus aureus*, coagulase positive, in colonies too numerous to count. Penicillin, 10,000 units, was started intramuscularly every three hours; sulfadiazine was continued.

The temperature continued to rise daily to 103° and 104° F., and the patient developed a subcutaneous abscess over the upper tibia of the right leg. In addition there developed considerable edema of the scrotum and legs, especially of the right knee. Repeated blood cultures showed hemolytic *Staph aureus* colonies, and the penicillin dosage was increased to 100,000 units every three hours. On the eighth hospital day the infant developed swelling and redness of the right wrist joint and swelling of the shoulders with further edema and evidence of involvement of the hips and right knee joint.

X-rays taken two weeks after admission showed destructive lesions of the proximal metaphysis of both femora, both humeri, and the distal metaphysis of the right radius and right femur. The film of the chest showed scattered densities in both lung fields, more pronounced on the left upper lobe. These were considered to be lung abscesses.

The child became worse and during the third week of hospitalization appeared moribund. The temperature fluctuated between normal and subnormal. Blood cultures continued to show *Staph aureus* in spite of 800,000 units of penicillin and one gram of sulfadiazine daily. Aspiration of an abscess over the sternum and of the right knee revealed thin green pus which on culture grew *Staph aureus*.

At the end of the fourth week of hospitalization the child appeared slightly better. His weight was 7 pounds and he began to take nourishment by mouth, but his general condition was so poor that little hope was held out for recovery. X-rays showed some indication of healing of the osteomyelitic lesions with bilateral dislocation of the hips and destruction of much of the neck and trochanteric areas. A blood culture at this time showed no growth, so it was decided to discontinue all medication.

The child remained about the same during the following week and then gradually began to recover. The legs were immobilized in traction to attempt to correct the flexion deformities, but as the swelling subsided and the general condition improved the child was allowed maximum motion. Immobilization of the hip in plaster was contemplated in order to keep the capital epiphysis, if it should regenerate, in the acetabulum, but it was decided to permit the child to move about to regain as much joint motion as possible. The consensus of the staff was that the joints were completely destroyed.

After discharge the baby was returned in one month because of a swelling and tenderness of the left wrist. As the child was otherwise well this was not treated and he was discharged home. Subsequent follow-up studies at 6 months showed a healthy-appearing child, weighing 12 pounds. X-rays showed deformity of the heads of both humeri, bilateral dislocated hips with deformity and absence of the femoral heads, and deformity of the right knee and wrist. There was complete fibrous ankylosis of the right hip joint with leg in abduction and 45 degree external rotation. Surgical intervention would probably be required to correct this at a later age.

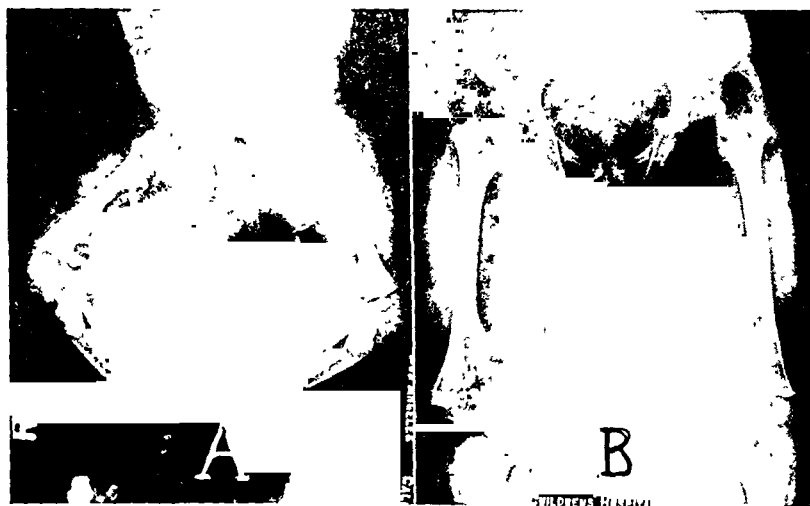


Fig. 1.—Roentgenograms of R. R. A, During the acute phase of his osteomyelitis. B, Film taken two years later. Note the deformity of the hip joints with absence of the capital femoral epiphysis. He had similar deformities of the proximal humeral epiphyses.

CASE 2.—Another infant, R. R., was admitted at 4 weeks of age with a history of a two weeks' illness prior to admission which was manifest by loss of appetite and weight, fever, irritability, and distress on motion of the extremities. His hospital course was very similar to that of J. A. With the aid of large doses of penicillin, sulfadiazine, and intravenous supportive therapy, he recovered from a hemolytic staphylococcus septicemia and multiple osteomyelitic abscesses involving both femora and humeri. In this case, in the fourth week of hospitalization the subcutaneous abscesses communicating with the bone and the joint abscesses were incised to establish drainage. For six weeks his rectal temperature spiked to elevations of 101° or 102° F. daily, and his leucocyte count ranged from 15,000 to 30,000. He was hospitalized for seven months.

During a follow-up period of three years' duration he developed no recurrence of the infection, had no draining sinuses, but demonstrated severe deformities and disabilities which resulted from the destruction of the metaphyseal and epiphyseal areas of the humeri and femori during the acute phase of the disease. (See Figs. 1 and 2.)

It is not to be concluded that all cases of osteomyelitis in infants followed the clinical course outlined. There were cases scattered along the scale of

severity; indeed, there were several with symptoms of inflammation near a joint, which subsided so rapidly with large doses of penicillin and sulfadiazine that the diagnosis of osteomyelitis can be suggested only tentatively by the clinical picture, since roentgenographic changes in the metaphyseal area of the bone never became apparent. These cases are not included in this study.

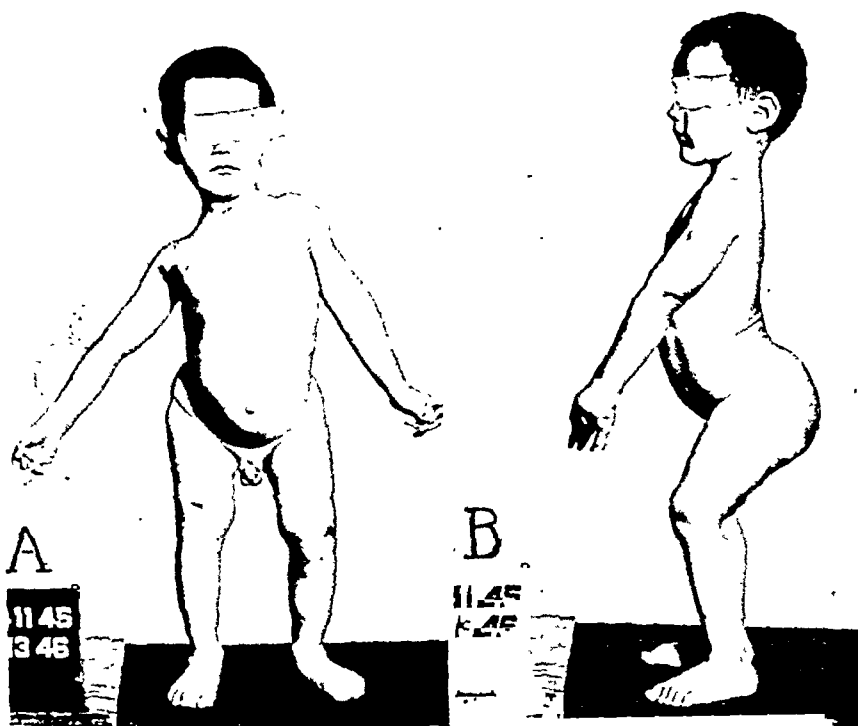


Fig. 2.—Deformities which R. R. presents two years after osteomyelitis involving the hips, shoulder, and right knee joint.

The clinical course in those cases of moderate severity tended to conform with that described by previous observers. The patients exhibited little general reaction to infection, and with the exception of the processes of repair in response to local damage to bone, evidenced few of the signs of a generalized infectious process. The term "benign" could perhaps be used in describing the type of clinical course these patients followed. The case of C. S. will serve to illustrate this type of infection.

CASE 3.—A 3-week-old male infant was admitted to the hospital because of failure to eat properly and swelling of the right hip region. Except for inflammation of the circumcision wound, for which he had been receiving boric compresses, the child had been well. On physical examination the child appeared normal. He held the hips flexed and cried when they were extended. Roentgenograms on admission revealed periosteal reaction of the proximal end of the right femur and evidence of displacement of the femoral heads. (See Fig. 4.) The blood culture grew hemolytic *Staph. aureus*, coagulase-positive.

The patient was placed on 40,000 units of penicillin intramuscularly every three hours and sulfadiazine, 0.5 Gm. daily. His legs were placed in traction. The child never appeared

ill, the temperature remained normal, and in three weeks signs of joint inflammation had completely subsided. Subsequent roentgenograms revealed no further destruction and healing of the osseous lesion.

One year later the infant had normal appearing hips on roentgenogram, a complete range of motion, and full use of his legs.



Fig. 3.—Comparison of a film of a congenitally dislocated hip with that of an inflammatory process of the hip joint. Top. In congenital dislocation the femur is displaced laterally and inferiorly, and the acetabular shadow is normal in its configuration. Bottom. In inflammatory process of the hip joint the femur is displaced laterally and inferiorly, and the acetabular shadow is normal in its configuration.

A satisfactory explanation of the recent appearance of the severely disabling and deforming cases of osteomyelitis among infants can be made by a comparative analysis of the mortality rate before and since both penicillin and sulfa derivatives have been available for treatment.

In a study conducted before the introduction of these therapeutic agents, Green⁵ found a mortality rate of 40 per cent in infants under 2 years of age. Among these cases the streptococcus was the most common etiological agent. Dunham¹ stated that 70 per cent of the infants with hemolytic *Staph. aureus* septicemia succumbed. Other authors do not report a mortality rate.

Between 1934 and 1943 there were twelve cases of hemolytic staphylococcus osteomyelitis in infants under 6 months of age admitted to the Children's Hospital. Seven of these infants died, a mortality rate of 58 per cent. For comparative reasons, cases due to the streptococcus were excluded since no cases due



Fig. 4.—Two films of dislocation of the hips with inflammation. Top: C. S. Bilateral osteomyelitis of the hips. The left hip already shows metaphyseal destruction and periosteal reaction. Bottom: Roentgenogram six months after osteomyelitis of the left hip showing persistence of the lateral and inferior displacement of the shaft of the femur. Note the position of the area of calcification in the epiphysis.

to this organism were treated after 1943. Two patients died shortly after admission without sufficiently characteristic roentgenographic evidence to make certain of the diagnosis. These patients are included in the series because with positive blood culture and evidence of joint involvement it is presumed that had they survived longer they also would have developed roentgenographic evidence of the disease. All others showed osteomyelitic processes on roentgenograms. Treatment consisted of supportive measures, incision and drainage of the abscesses, and in the later years, the sulfa derivatives.

None of the five survivors of this group suffered a stormy or prolonged clinical course, and subsequent examinations revealed no severe deformities or osteomyelitic residua to be present. Their infections were apparently mild and their course of the "benign" form.

Between 1943 and 1947 six cases of osteomyelitis in infants under 6 months of age were admitted to the Children's Hospital. They were all due to the staphylococcus. The absence of osteomyelitis due to the streptococcus as reported in earlier observations may be a result of the efficacy of the new drugs in controlling such infection. All of the patients admitted after 1943 received large doses of penicillin and sulfadiazine; one 6 pound infant received as high as 800,000 units of penicillin a day. There were no deaths during this period, a mortality rate of zero as compared with a previous mortality rate of 58 per cent. Of these six patients two showed severe bone damage and deformity, two, residual deformity of one joint, and two, complete recovery.

It seems logical, from comparison of the mortality rate in these two groups, to postulate that the two patients in the second group who exhibited the severe form of the infection and disabling deformities probably represent that group of infants which, prior to the introduction of penicillin, succumbed. Likewise it seems reasonable to suggest that with an increased survival rate which present methods of therapy are effecting, an increase in the number of cases with severe systemic reactions and permanent bone deformity and disability might be expected.

Early diagnosis with institution of adequate therapeutic measures is of primary importance in reducing the mortality rate and serious sequelae of osteomyelitis in the newborn infant.

The diagnosis of osteomyelitis in the newborn child is frequently masked by a lack of any specific reaction to infection by the infant. In the presence of septicemia and overwhelming infection, the temperature and leucocyte count may approximate normal, while the patient exhibits signs of gastrointestinal irritation or demonstrates signs of a feeding problem. Evidence of bony involvement may not be apparent unless specifically searched for, because of the obscuring fatty subcutaneous tissues and the characteristic flexed position of the lower extremities in the newborn infant. Perhaps the most important aids at this early stage are blood cultures and roentgenograms. The growth of an organism from a venous blood sample may be the first significant clue as to the disease process.

Roentgenograms usually do not show changes at the epiphyseal areas during the first stages of the disease. About one week's time is usually required for periosteal elevation and areas of bone formation and destruction to progress sufficiently to be visualized on the roentgenograms. There is, however, one significant finding in films taken early in the course of infection, and that is widening of the joint space.

Ninety per cent of our cases showed involvement of a hip joint. In infants, the capital femoral epiphysis is not visualized roentgenographically until about 6 months of age. The shaft and metaphyseal area are visualized, however, and bear a definite relation to the x-ray shadow cast by the bony structures of the

pelvis. In the early stage of osteomyelitis of the proximal end of the shaft of the femur, the inflammatory exudates tend to gather in the hip joint capsule and to distend the joint. This distention, probably in combination with capsular changes, produces a lateral displacement or lateral dislocation of the head of the femur from the acetabulum. This dislocation is the earliest roentgenographic finding and should cause one to suspect an inflammatory process in and about the joint.

Congenital dislocation of the hip may be confused with this lateral dislocation of the hip. A differentiation between the two, however, may be made on examination of the acetabular roof. In congenital hips, the roof or horizontal portion of the acetabulum tends to be more vertical and the lateral lip compressed and deformed by pressure of the head, whereas in inflammatory dislocations, the acetabulum is normal in its roentgenographic appearance. This feature, combined with evidence of soft tissue swelling, will generally serve to differentiate the two conditions. (See Figs. 3 and 4.)

In the majority of cases of osteomyelitis in the newborn infant there has been some antecedent infection, usually omphalitis, infection of a circumcision wound, impetigo, or a staphylococcus nasopharyngitis. The proper control and intensive treatment of these lesions with all available aids will probably offer us our best chance to prevent septicemia and its disabling sequelae.

SUMMARY

1. Osteomyelitis in the infant should not be considered a benign infection.
2. All minor infections in the newborn infant should be considered precursors of severe infection and treated accordingly.
3. Every effort should be made toward early diagnosis and control of the blood stream infection and the bony lesions in osteomyelitis because of the possibility of death or disabling deformity which may occur.
4. Roentgenographic changes which suggest the diagnosis and are seen in the early stages of the disease are described.
5. While the mortality rate is approaching zero in osteomyelitic infections, the number of cases with severe bone damage and its subsequent disability is becoming greater. In view of this change the prognosis for complete recovery without deformity should be held in abeyance, especially in the severe type of infection.

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RELATIONSHIP OF RACE TO THE INCIDENCE OF DIPHTHERIA AND TO SCHICK, TUBERCULIN, AND WASSERMANN TESTS IN HOSPITALIZED CHILDREN

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THE statement often has been made that diphtheria is less frequently seen in Negro than in white children and that the reverse is true of tuberculosis and syphilis. Is this race variation due to a difference in susceptibility or to greater exposure from the marked overcrowding and poor living conditions of the Negro children, or are the milder cases overlooked? In an attempt to answer this question, the incidence of diphtheria and the percentages of positive Schick, tuberculin, and serologic tests for syphilis of the white and Negro children admitted to Duke Hospital from 1932 to 1939 were tabulated (Table I). As these children, who came from practically every county in North Carolina, were hospital patients, the figures may not be an accurate index of the incidence of diphtheria, tuberculosis, and syphilis, yet they are similar to the death rates from these diseases in children throughout the state (Table II).

TABLE I. RELATIONSHIP OF RACE TO TUBERCULIN, SCHICK, AND WASSERMANN TESTS
(1932 to 1939)

	WHITE	NEGRO
Diphtheria	(1,261 patients) 63 or 5.2%	(518 patients) 18 or 3.6%
Positive Schick tests	(1,644 patients) 253 or 15.4%	(642 patients) 85 or 11.6%
Positive tuberculin tests	(1,751 patients) 90 or 5.1%	(684 patients) 95 or 13.8%
Positive serologic tests for syphilis	(1,196 patients) 12 or 1%	(496 patients) 39 or 7.8%

TABLE II. MORTALITY RATES IN NORTH CAROLINA FOR 1938 (BIRTH TO 14 YEARS)*

	WHITE	NEGRO
Diphtheria	143	25
Tuberculosis (all types)	33	75
Syphilis	27	92

*Per 100,000 of population.

The incidence of clinical diphtheria in the Negro children in this series is 69 per cent of that in the white children (3.6 to 5.2 per cent; Table I), and the susceptibility to diphtheria in the Negro children is 75 per cent of that in the white children (positive Schick tests, 11.6 to 15.4 per cent; Table I). These percentages are so similar that it would seem that the lower incidence of diphtheria in Negro children is due to their lower susceptibility rather than to the overlooking of mild cases. That the death rate from diphtheria in Negro

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children is only 48 per cent of that in white children (2.8 to 5.8 per 100,000; Table II) also may be due to this apparently lower susceptibility, though undiagnosed cases cannot be excluded as an explanation.

The incidence of tuberculous infections in the white children in this series is 37 per cent of that in the Negro children (positive tuberculin tests, 5.1 to 13.8 per cent; Table I), and the death rate from tuberculosis in the white children is 17 per cent of that in the Negro children (1.3 to 7.5 per 100,000; Table II). These lower tuberculosis figures in the white children probably indicate a lower susceptibility to tuberculosis, although they also may be explained by a lower rate of exposure.

The incidence of syphilis in the white children in this series is 13 per cent of that in the Negro children (positive serologic tests 1 to 7.8 per cent; Table I), and the mortality from syphilis in the white children is 11 per cent of that in Negro children (1 to 9.2 per 100,000; Table II). These lower syphilis figures in the white children probably are due to a lower rate of exposure to syphilis, though a lower susceptibility also may be the cause.

VARICELLIFORM ERUPTION OF KAPOSI DUE TO VACCINIA VIRUS COMPLICATING ATOPIC ECZEMA

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SIXTEEN eczematous patients with a varicelliform eruption characteristic of that described by Kaposi have been observed by us.

These patients were part of an unique outbreak of forty-three cases, the first epidemic to be recorded in the United States, which occurred in New York City during May, 1947.¹ In the past, rare "epidemics" have occurred,²⁻⁵ but most reported cases have been sporadic in frequency.

Prior to this outbreak, a mass vaccination campaign against smallpox was conducted in New York City. By the end of April, 1947, an estimated 6,350,000 inhabitants had been vaccinated.¹ The incidence of varicelliform eruption was approximately one case to 150,000 vaccinations.

There was a definite time relationship between the mass vaccinations and the outbreak of Kaposi's varicelliform eruption. This disease started with dramatic suddenness three weeks after the beginning of the vaccination campaign and ceased with equal abruptness three weeks after the campaign was over.

Kaposi, in 1887, gave a classical description of this varicelliform eruption: "An acute outbreak of numerous vesicles . . . the majority are umbilicated . . . They look like varicella vesicles . . . The vesicles develop very acutely (sometimes overnight) . . . Those which appear first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off . . . The largest of the varicella-like vesicles are found upon the already eczematous skin, but smaller groups appear upon the intact skin of the neighborhood . . . In many places pigment patches are left over, or even flat cicatrices."⁶ Although Kaposi made no bacteriologic studies, he was of the opinion that a fungus was the causative agent.

During the next few decades interest in this disease was spasmodic.⁷⁻¹³ Approximately forty years later, McLachlan and Gillespie described the first "epidemic" and suggested that a streptococcus was the etiological agent.² Ellis¹⁴ and Freund⁹ found Guarnieri's bodies in a biopsy specimen and were among the first to hint that the etiological organism might be a virus. Tedder, in 1936,¹⁵ expressed the belief that Kaposi's varicelliform eruption and eczema vaccinatum were identical, and pointed out that Martin¹⁶ had described a case of eczema vaccinatum prior to Kaposi, in 1882.

Scattered reports continued to appear in the literature,¹⁷⁻²² but only in the past seven years has this syndrome emerged as a clinical entity. Esser²³ reported on four patients in 1941 from whom the virus of herpes simplex was recovered and identified by Seidenberg.²¹ In 1943, Ronchese²⁵ reported two cases, one of which he thought due to the virus of vaccinia. Strickler³ in 1944 reported on five children, all of whom had had contact with vaccinia virus. Barton and

Brunsting,²⁶ Wenner,²⁷ Lynch and Steves,²⁸ Blattner and associates,²⁹ Lane and Herold,³⁰ and Jaquette and co-workers³¹ have recently reported on immunologic and virus studies incriminating the herpes simplex virus as the causative agent. Hershey and Smith³² presented cases and performed similar immunologic studies in 1945, implicating the vaccinia virus as the etiological agent of Kaposi's varicelliform eruption.

CLINICAL MANIFESTATIONS

Sixteen children with atopic eczema and a complicating varicelliform rash were admitted within a five-week period to a ward of the Kingston Avenue Hospital for Contagious Diseases. Hospitalization, as a rule, occurred two or three days after the onset of the new eruption. The constitutional reactions, which had been mild at the onset of the eruption, suddenly became severe about the third day with the appearance of high fever, restlessness, irritability, anorexia, and facial edema, which were the symptoms on admission. In all instances pruritis was intense, and the resultant scratching had frequently denuded large areas of skin on the face.

All sixteen children had been recently exposed (Table I) to a freshly vaccinated individual (parent, sibling, or nurse). In some instances, there was more than one such contact.

The course divided itself into three phases: the acute febrile, the healing, and the convalescent periods. Each was of approximately one week's duration. However, in a few instances convalescence was prolonged, due to the severity of the disease and complicating infections.

In thirteen of the patients, the febrile phase lasted from five to seven days, the temperature varying between 102° and 104° F., and dropping by lysis. In two instances, the temperature was within normal limits by the third day, and in one, was prolonged for three weeks. The latter was an extremely severe case (B. A., Fig. 5) with a *concomitant confluent bronchopneumonia* which progressed to circulatory collapse with pulmonary edema.

The eruption, confined almost entirely to the eczematous areas, was essentially pustular and had many similarities with vaccinia, varicella, and variola. At the onset, crops of vesicles and pustules, about 5 mm. in size and frequently umbilicated, were noted. These became larger, showing a tendency to coalesce. Some lesions were almost bullous in size and could have been mistaken for those of variola. There was a subsequent spread to the neck and, in diminishing intensity, to the upper extremities, anterior thorax, and lower extremities. Occasionally the abdomen and back were also involved. Although within two days after the appearance of the lesions, scab formation occurred, new crops of the eruption were still appearing up to the fourth day of hospitalization.

There was marked cellulitis of the face and edema of the eyes which subsided slowly but completely in a week. Frequently, this edema closed the eyes so completely that it was impossible to inspect the conjunctiva.

The enlargement of the lymphatic glands immediately draining the regions involved by the eruption was striking. Although several of these nodes became fluctuant, they receded spontaneously.

TABLE I. SUMMARY OF CLINICAL AND LABORATORY DATA ON SIXTEEN CASES OF KAPOSI'S VARICELLIFORM ERUPTION

CASE	AGE	SEX	RACE	VACCINIA CONTACTS	PERIOD OF INCUBATION* (DAYS)	VACCINATION PRIOR TO ADMISSION	COMPLICATIONS	HIGHEST BLOOD EOSINOPHILIA (%)
1. F. W.	15 mo.	M	Negro	2—Mother, aunt	12	Not vaccinated	Bronchopneumonia, alopecia	12
2. R. S.	7 mo.	M	Negro	1—Mother	Unknown	Not vaccinated	Bronchopneumonia, alopecia	14
3. E. C.	1 yr.	M	Negro	3—Mother, father, sibling	5	Not vaccinated	None	18
4. M. S.	20 mo.	F	Negro	5—Mother, father, siblings	10	Not vaccinated	Alopecia	16
5. B. A.	7 yr.	M	White	3—Mother, aunt, friend	9	Not vaccinated	Bronchopneumonia, circulatory collapse, alopecia	18
6. D. H.	7 mo.	F	Negro	7—Mother, siblings	15	Not vaccinated	Bronchopneumonia, alopecia	34
7. F. S.	10 mo.	M	White	8—Mother, father, siblings	15	Not vaccinated	Alopecia	38
8. A. B.	4 yr.	M	Negro	Hospital nurses and attendants†		Vaccinated 3 yr. previously	Bronchopneumonia	52
9. E. R.	3 yr.	M	Negro	2—Mother, sibling	7	Not vaccinated	Bronchopneumonia	12
10. M. H.†	1 yr.	M	Negro	2—Mother, aunt	13	Not vaccinated	Alopecia, diarrhea	4
11. G. H.†	2 yr.	M	Negro	2—Mother, aunt	13	Not vaccinated	Bronchopneumonia, diarrhea, alopecia, bilateral purulent otitis media	4
12. R. H.†	3 yr.	M	Negro	2—Mother, aunt	13	Not vaccinated	Bronchopneumonia, pharyngitis	14
13. J. Z.	8 mo.	M	White	Hospital nurses and attendants†		Not vaccinated	Alopecia	22
14. D. T.	2 yr.	M	Negro	2—Mother, sibling	19	Not vaccinated	None	2
15. V. S.	4 mo.	F	Negro	Hospital nurses and attendants†		Not vaccinated	None	10
16. D. A.	1 mo.	M	Negro	1—Mother	7	Not vaccinated	Bronchopneumonia	14

An impressive manifestation at this time was the marked regression of the eczema.

The healing stage was characterized by a gradual shedding of the crusts, occasionally exposing bleeding, raw, granular surfaces. By the second week of hospitalization the lesions were all healed, resulting in small, flat, smooth, depigmented scars.

Convalescence was rapid with complete healing of the remaining lesions. The eczema, which had improved in the majority of patients during the febrile phase, now returned.

Complications.—(See Table I.) Roentgenograms of the chest were taken of all but one patient at several intervals during hospitalization. Seven of the patients showed patches of bronchopneumonia during the acute episode. One patient had a right confluent infiltration, while another had multiple lobular infiltrations of the lower two-thirds of both lung fields.

Alopecia in ten patients varied from slight to complete loss of hair. It involved chiefly the temples and occipital regions, and was patchy in character. There was no regrowth up to the time of discharge eight weeks later, but within four months, five of these patients had a complete return of hair. Previously, only one case with this complication had been reported; this patient showed a complete regrowth of hair in six months.²⁵

Purulent otitis media, diarrhea, and pharyngitis were also observed.

Incubation Period.—The period of incubation (Table I) averaged 10.6 days with a variation of 5 to 19 days. McLachlan² was one of the very few authors to give incubation periods; in his cases the average was 12.5 days with a variation of 8 to 18 days.

TREATMENT

Immediately after hospitalization, all patients were placed on a regime of 50,000 units of penicillin intramuscularly every three hours, to control possible secondary infections. This schedule was maintained until they were afebrile for at least forty-eight hours.

Wet compresses saturated with aluminum acetate (Burow's) solution, diluted 1:20 parts, were applied to the involved skin areas to inhibit local spread and to diminish edema of the underlying tissues.

The prevention of scratching was found to be extremely important. The extremities were restrained, the fingernails cut short, and roentgenographic film (emulsion removed) was placed under the head to minimize friction.

REPORT OF A TYPICAL CASE

F. S., a 10-month-old white male infant, was admitted on May 8, 1947, with a history of rash and fever of three days' duration.

This patient had never been vaccinated. However, eight members of the household (parents and siblings) had been vaccinated successfully about three weeks prior to the onset of the patient's illness.

There was a positive family history for allergy, the maternal grandmother having hay fever.

The infant had had an eczema since the age of 8 months, starting on the cheeks and spreading in two months to involve face, neck, chest, and extremities. The parents had noted that the rash always increased in severity following ingestion of cereal.

During the three days prior to hospital admission, coincident with the onset of fever, a secondary rash appeared on the eczematous skin. Because of the increasing severity of the illness, the child was hospitalized.

On admission, the patient was acutely ill and had a temperature of 103° F. The integument of the face, neck, chest, and extremities appeared lichenified. In addition, the face was covered with vesicles and pustules, many of which were umbilicated. These varied from 2 to 8 mm. in diameter. The profuse secondary lesions were confined mainly to the eczematous areas. The eyelids were edematous and closed. The cervical, axillary, and inguinal lymph nodes were markedly enlarged. As a result of the scratching incident to the intense pruritis, parts of the face were denuded and bleeding.



Fig. 1.

Fig. 1.—(V. J.) Second hospital day. Typical umbilicated papular and pustular lesions which appeared in thirty-six hours. Note large lymph node in axilla.



Fig. 2.

Fig. 2.—(V. J.) Fourth hospital day. Same patient and area as in Fig. 1 forty-eight hours later. Lesions have rapidly become flat and crusted.

The temperature ran a septic course, varying between 102° and 104° F., and approaching normal limits on the seventh day. During the febrile stage there was a considerable remission of the eczema. It reappeared gradually after the subsidence of the fever. On the third day of hospitalization most of the lesions were crusted; by the seventh day the edema had subsided; by the fifteenth day the denuded areas were no longer bleeding and weeping, and all the crusts had fallen off, leaving behind depigmented, small, smooth cicatrices. A moderate alopecia of the temples and occiput was first evidenced about the fourteenth day of hospitalization.

On the day of admission, the white blood count was 17,000; polymorphonuclear leucocytes, 40 per cent; lymphocytes, 48 per cent; and eosinophiles, 12 per cent. After the acute stage (tenth day) the white blood count dropped to 11,000, with a rise in lymphocytes to 92 per cent. By the third week, the blood count and differential were essentially normal with the exception of an eosinophilia of 14 per cent.

Treatment consisted of wet dressings of aluminum acetate solution and intramuscular injections of 50,000 units of penicillin every three hours.

During the third week of hospitalization, the patient was vaccinated and developed an immune reaction.

The patient was discharged June 19, 1947, completely well except for eczema and very small, smooth, depigmented scars.

LABORATORY FINDINGS

On admission, thirteen patients had a white blood cell count which varied from 13,000 to 24,000, while three had counts between 7,000 and 8,000. During the first week, none of the patients had the pronounced leucopenia described by some authors.^{29, 30} However during the second week of hospitalization, six of the patients developed a slight transient leucopenia, between 4,000 and 5,000. Initially, in twelve patients the polymorphonuclear neutrophile count varied between 40 and 60 per cent, but, curiously, in eleven instances, following the institution of penicillin therapy, the lymphocytes increased and the neutrophils became depressed to a marked degree, even though the total count of white blood cells remained the same or was increased.



Fig. 3.

Fig. 3.—(G. H.) First hospital day. Very early vesicular lesions on forehead. Umbilicated papules noted on edematous eyelids.



Fig. 4.

Fig. 4.—(M. H.) Third hospital day. Typical facies showing eruption superimposed on the eczema and a denuded area over the closed eye.

A moderate to marked hypochromic anemia of the blood was frequently present. However, this was not more marked than one would expect with severe fever.

Convulsions and encephalitic changes noted at post-mortem have been reported by several authors.^{17, 23, 27} Although no neurological signs were seen in our series, we felt that spinal fluid studies might be informative. Spinal taps were performed on four patients during the acute phase of their illness, and on two during the convalescent stage. The cell counts and chemistries were all within normal limits.

The urine was negative as a rule, several of our patients showing only transient traces of albumin.

Blood agar cultures were taken from early vesicular lesions of three patients. *Staphylococcus albus* was cultured from two, and *Streptococcus haemolyticus* from the third. We are in agreement with recent authors^{14, 26, 31} who believe that these organisms are secondary invaders.

ALLERGIC BACKGROUND

A constant finding in every patient was the association of atopic eczema of moderate or severe degree. The absence of other dermatoses described by previous authors^{2, 5, 33} (acne, scabies, impetigo, burns) is noteworthy.

A history of infantile eczema was obtained in every case by a personal interview with one of the parents. The eczema, in each case, started on the cheeks before the age of 8 months, later spreading to the neck, chest, and extremities. This may explain in part the predominance of the outbreak of Kaposi's disease in children under 2 years. In one-third of the cases, the lichenification of the skin was generalized at the time of hospital admission.



Fig. 5.

Fig. 6.

Fig. 5.—(B. A.) Seventh hospital day. Eczema has subsided and lesions are crusted. Alopecia starting at temples.

Fig. 6.—(B. A.) Seventeenth hospital day. Exacerbation of eczema and marked alopecia ten days later.

Ten patients (63 per cent) had a definite history of allergic manifestations to specific foods, and one child had asthma. Furthermore, an immediate family history of allergy (asthma, hay fever, or atopic eczema) was obtained in ten cases.

During the acute phase of the varicelliform eruption, the hospital laboratory reported eosinophilic counts ranging from 10 to 52 per cent in thirteen of the patients (Table I).

AGE, RACE, AND SEX

This disease is generally encountered in infants and children (Table II). Eleven (70 per cent) of our cases occurred in children under 2 years of age. The remaining five ranged up to 7 years of age. Although this disease has been reported in adults,^{34, 35} none was observed in our series.

Thirteen children were Negro and three were white. It would seem more likely that this predominance of Negroes was the result of the poor sanitation and overcrowding characteristic of the living conditions of this group, rather than any inherent race susceptibility.

Thirteen (80 per cent) patients were males. This predominance may be unduly high compared with Barton and Brunsting's review of the literature stating: "Of the 50 patients for whom sex was listed, 30 were males and 20 were females."²⁶

MORTALITY AND MORBIDITY

There were no deaths in the sixteen patients under our observation, and the mortality among the forty-three patients in New York City was 4 per cent. This contrasts sharply with the 20 per cent mortality calculated on the eighty-two cases which we found recorded in the literature. McLauchlan² reported five deaths in his series of sixteen cases—the largest epidemic prior to the recent outbreak.

Since practically all of our patients were extremely toxic, one can speculate whether the method of therapy, including the use of penicillin for the control of secondary invaders, was the important factor in the reduction of mortality.

DISCUSSION

Since Kaposi first described this disease, many conflicting and contradictory reports have been written regarding its etiology. We suggest that it be considered an exanthem peculiar to atopic persons with allergic eczema, the etiology of which may be the virus of vaccinia, herpes simplex, or possibly others. The nomenclature "eczema herpetiformis" and "eczema vacciniformis" might be more specific in differentiating the two known types.

For the purpose of determining the specific immunity produced in our series of patients, we vaccinated fifteen of the sixteen about four weeks after admission. We used several different fresh vaccinal preparations known to produce "takes," employing scratch or multiple puncture methods. All of the patients developed immune reactions consisting of a small papule at the site of inoculation within the first forty-eight hours. Since these patients had not been vaccinated previously, this reaction was evidence of a high degree of immunity induced by their illness. The type of immunity produced and the relationship of this large outbreak to over six million vaccinations offered excellent, though indirect, evidence that the vaccinia virus was the etiological agent.

We are in agreement with the authors who believe that eczema vaccinatum, variola pustulosis acuta, and Kaposi's varicelliform eruption are identical,^{15, 29} as differentiated from generalized vaccinia. Although the rash and many of the other characteristics of Kaposi's varicelliform eruption resemble variola more than varicella, the term "varicelliform eruption" probably should be retained because of its accepted usage.

Comparison of our cases of "eczema vacciniformis" to reported cases of "eczema herpetiformis" leads us to the impression that clinically the two types are identical. Laboratory procedures such as mouse protection tests, trial vaccinations, chick embryo inoculations, or perhaps examination by the electronic microscope would be required to differentiate the two types.

Our study of these patients gives us the impression that primary inoculation of the virus is through the eczematous, damaged skin from some external contact, and that lack of specific immunity to the etiological virus in these unvaccinated individuals accounts for the unusual severity of this disease (heavy

TABLE II. SUMMARY OF REPORTED CASES OF KAPOSI'S VARICELLIFORM ERUPTION

AUTHOR	NUMBER OF CASES	AGES	CONTACT WITH HERPES SIMPLEX OR VACCINIA	VIRUS IDENTIFIED	MORTALITY	ANTECEDENT RASH
Kaposi ⁶ (1887)	10	Not known	Not known	No	1	Atopic eczema
Juliusberg ⁷ (1898)	1	1½ yr.	Vaccinated mother	No	1	Atopic eczema
Freud ¹¹ (1931)	1	6 mo.	Not known	No	1	Atopic eczema
Frühwald ⁸ (1931)	2	18 to 20 yr.	Not known	No	0	Atopic eczema, seborrheic eczema
Freund ⁹ (1934)	1	2½ yr.	Not known	Positive Paul test	0	Atopic eczema
Goeckerman and Wilhelm ²⁰ (1935)	1	32 yr.	Not known	No	0	Atopic eczema
Corson and Ludy ³⁹ (1935)	3	1 to 9 yr.	Not known	No	0	Atopic eczema
Ellis ¹⁴ (1935)	2	3 yr. (twins)	Vaccinated brother	Guarnieri bodies	1	Atopic eczema
McLachlan and Gillespie ² (1936)	16	3 wk. to 7 yr.	Not known	No	5	Atopic eczema, impetigo, scabies, seborrheic eczema
Tedder ¹⁵ (1936)	1	5 mo.	Vaccinated brother	No	1	Atopic eczema
Nimpfer ⁵ (1936)	4	Not known	Vaccinated patient	No	0	Burn
Brain and Lewis ¹⁸ (1937)	1	15 yr.	Not known	No	1	Atopic eczema
Schwartz ⁴³ (1939)	1	32 yr.	Not known	No	0	Atopic eczema
King ¹⁷ (1939)	5	6 mo. to 72 yr.	Not known	No	2	Atopic eczema
Bettley ¹⁹ (1940)	1	1 yr.	Not known	No	0	Atopic eczema
Esser ²³ (1941)	4	Infants	Not known	Herpes simplex in two cases	1	Atopic eczema
Pepple et al. ³⁵ (1942)	3	17 mo. to 36 yr.	Not known	Guarnieri bodies in one case	0	Atopic eczema
Barton and Brunsting ²⁶ (1944)	1	30 yr.	Not known	No	0	Atopic eczema
Ronchese ²⁵ (1943)	2	15 to 20 mo.	Vaccinated siblings in one case	One patient vaccinated subsequently unsuccessfully	1	Atopic eczema
Blattner et al. ²⁹ (1944)	1	15 mo.	Not known	Herpes simplex	0	Atopic eczema
Lane and Herold ³⁰ (1944)	5	15 mo. to 20 yr.	Not known	Herpes simplex in one case; another case vaccinated successfully 5 mo. later	0	Atopic eczema
Wenner ²⁷ (1944)	3	5 to 20 mo.	Not known	Herpes simplex in three cases	1	Atopic eczema
Barton and Brunsting ²⁶ (1944)	2	21 yr. and 30 yr.	Not known	Herpes simplex in one case	1	Atopic eczema
Lynch ⁴¹ (1945)	4	10 mo. to 54 yr.	Herpetic lesions in two cases and possibly in the third case	Herpes simplex in one case	0	Atopic eczema

TABLE II.—CONT'D

AUTHOR	NUMBER OF CASES	AGES	CONTACT WITH HERPES SIMPLEX OR VACCINIA	VIRUS IDENTIFIED	MORTALITY	ANTECEDENT RASH
5. Ebert ⁴² (1945)	1	Adult	Not known	Herpes simplex	0	Not known
6. Hershey and Smith ³² (1945)	1	12 mo.	Vaccinated brother	Vaccinia	0	Atopic eczema
7. Jaquette et al. ³¹ (1946)	1	6 mo.	Vaccinated brother	Herpes simplex	0	Atopic eczema
8. Lynch and Steves ²⁸ (1947)	4	20 to 69 yr.	Not known	Herpes simplex in one case	0	Atopic eczema and acne

clustering of lesions and marked systemic symptoms). In contrast, generalized vaccinia may result from autoinoculation, and furthermore, it requires no pre-existing rash. We have found no recorded instance of Kaposi's varicelliform eruption in a recently vaccinated individual, nor could we find one of autoinoculation.

The methods of contagion are not definitely known. Direct contact and nasal droplets³⁶ both probably play a part. According to some evidence, fomites²² and urine³⁷ could also be vectors.

Clinically and experimentally the vaccinia virus seems to be dermatotropic for "damaged" skin,^{38, 39, 40} particularly the injured eczematous skin of an atopic individual. In this epidemic, the eczematous patients had been exposed to a tremendously increased number of contacts incident to the vaccination campaign. Since, customarily, patients with eczema are not vaccinated, the resultant outbreak of this rare disease is explained.

The improvement of the eczema during the acute stage of the illness is a fairly well-known phenomenon and occurs in other acute febrile conditions.

SUMMARY

1. The characteristics of an epidemic of Kaposi's varicelliform eruption, probably due to vaccinia virus, are presented.
2. The elimination of mortality in our series is evidence of the efficacy of penicillin therapy in controlling secondary infections and complications.
3. The hypersusceptibility of the atopic child with eczematous skin to the vaccinia virus emphasizes the necessity of isolating such children from contact with recently vaccinated individuals.

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THE PROCTOLOGIC EXAMINATION OF INFANTS AND CHILDREN

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IN RECENT years attention has been occasionally called to the importance of the proctologic examination in infants and children. However, in spite of some valuable contributions, an entirely satisfactory approach to this examination has not been fully established. It is probable that because of the difficulties encountered in attempting to make the proctologic examination, many examiners have become discouraged and disinterested. The noteworthy reports of Paulson¹ and of Daniels² have been the first really stimulating contributions to an organized proctologic examination of infants and children. Paulson described a practical method for the examination, detailing the preparation, the position, the technique, and his equipment for the procedure. Daniels, besides giving the detailed anatomy of the terminal bowel, also described the preparation, position, and instruments used by him. Santamarina³ reported his methods and experiences in examining the rectum and sigmoid of eighty-four children.

For the past ten years at the Jewish Hospital of Brooklyn a definite plan has been carried out by the division of proctology for the special study of pediatric proctology. A cooperative program between this department and the pediatric department made it possible to examine over 500 children. The study embodied observations on the (1) methods of examination and the armamentarium. (2) anatomy of the terminal bowel, (3) x-ray studies and diagnosis of the large bowel, (4) proctologic conditions found, and (5) treatment.

The present report is concerned only with the methods and armamentarium used in the proctologic examination of infants and children. The routine examination consisted of: (1) history, (2) abdominal palpation, (3) perianal inspection and palpation, (4) digital examination, (5) anoscopy, (6) sigmoidoscopy, and (7) barium x-ray enema.

HISTORY

The following history form proved of inestimable value as an aid in examination and diagnosis:

RECORD OF PROCTOLOGIC EXAMINATION OF CHILDREN

NAME:	AGE:	SEX:	COLOR:	DATE:
ADDRESS:				
PEDIATRIC HISTORY:				
PROCTOLOGIC HISTORY:				
Bleeding	Pain	Protrusion		
Abscess	Discharge	Itching		
Diarrhea: no. movements	duration	constant		
blood pus	mucus	cramps		
Constipation		Previous treatment		

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From the Division of Proctology, Department of Surgery, Jewish Hospital of Brooklyn.

FINDINGS:

Abdomen:

Sacrum:

Sacrococegeal area:

Dimple

Swelling

Hairs

Discharge

Sinus

Perianal area:

Erosions

Eczema

Sinus

Scars

Abscess

Thrombosis

Swelling

Sphincters:

Relaxed

Spastic

Continent

Anus:

Ulcers

Scars

Fistulous openings

Thrombosis

Papillae

Crypts

Foreign body

Patency

Hemorrhoids

Discharges

Abscess

SIGMOIDOSCOPY: Size of scope

Position

Interference

Distance

Character of stool

Appearance of mucous membrane

Membrane (congenital)

Valves of Houston

New growths:

Fistulous openings

size location number

DIAGNOSIS:

TREATMENT:

ABDOMINAL PALPATION

Palpation of the abdomen before proceeding to the actual proctologic examination may give a clue to the diagnosis and explain the proctologic symptoms. Abdominal enlargement is seen in the celiac syndrome, severe rickets, tuberculous peritonitis, and Hirschsprung's disease. Splenomegaly can be due to sepsis, essential anemia, syphilis, erythroblastosis, or *hydrops foetalis universalis*. The liver is enlarged by sepsis, icterus, syphilis, or congenital cysts. Kidney enlargement can be found with congenital polycystic kidneys, hydronephrosis, or hypernephromas. Masses such as hypertrophied pylorus or intussusception can be detected. Rigidity will be caused by appendicitis, Meckel's diverticulum, and peritonitis.

PREPARATION

The patient is prepared for the examination by (A) a cleansing enema and (B) sedation.

After having encountered many difficulties during the examination it can now be definitely stated that the preparation for and the position of the patient during examination must be properly planned or the procedure is destined to fail. Nevertheless, with the understanding and use of the technique as herein outlined, the proctologic examination of young children becomes simplified.

A. Cleansing Enema.—There are various recommended plans for cleansing the lower portion of the bowels. Daniels orders an enema or a cathartic the night before and permits nothing by mouth for three hours before examination. Santamarina gives four enemas the day of the examination, and Paulson orders a saline enema several hours before.

Our routine instructions given in printed form to the patient are as follows:

1. *Evening before* the examination give your child one or two teaspoons of milk of magnesia. (Do not give this if your child has diarrhea.)
2. *Day of examination:*
 - a. For breakfast: orange juice and water only.

- b. Two hours before examination give the child an enema of two glasses of plain warm water, and add more water until the return is clear.
- c. A light lunch is allowed of fruit juice and soup, or cooked cereal and milk.
- d. Before leaving the house put the child on the toilet.
- e. Then insert into the child's rectum the suppository ordered.

Giving the enema two hours before the examination was found to be the best time; when longer periods were allowed, sufficient time elapsed for other stool to enter the rectal ampulla. If shorter periods were used, liquid stool remained in the rectum or the urge to move the bowels continued during the examination. Allowing food just before the examination comforts the child, yet does not stimulate peristalsis.

B. Sedation.—It is practically impossible to obtain sufficient cooperation from the conscious child to perform a satisfactory examination of the anorecto-sigmoid region. An unwilling, struggling child makes it difficult and dangerous to attempt the procedure. No doubt a general anesthesia is the ideal approach for this examination, but is it the most practical or safest to recommend for routine examination? Daniels recommends a general anesthesia. Objections to general anesthesia, aside from the persuasion necessary to gain assent from parents for a supposedly routine examination, is the danger of the anesthesia itself. Straining and vomiting occurring when the scope is in the bowel may cause trauma or perforation. This has occurred in the adult, and as the examination becomes a more common procedure in pediatrics, accidents will certainly occur unless the safest methods are established.

Morphine in carefully established doses is recommended by Paulson. He found that its hypodermic administration resulted in the control of the patient necessary for successful instrumentation. Undoubtedly morphine is safer and more practical than general anesthesia. However, infants and children are notoriously sensitive to morphine,⁴ in addition to which it has an unpredictable effect. Santamarina used Nembutal, and although he had some mild reactions in his eighty-four cases, he obtained complete cooperation during his examinations.

We have tried various medications to obtain the cooperation and relaxation of the child before examination. We finally decided upon our present plan of divided pre-examination medication as follows: (1) Before leaving home for the examination a nembutal suppository is inserted into the child's rectum. (2) Upon arriving at the office, or approximately one hour later, a subcutaneous injection of codeine sulfate and atropine sulfate is given (see Table I).

TABLE I PRE EXAMINATION MEDICATION

HOME MEDICATION (RECTAL)		OFFICE MEDICATION (HYPODERMIC)	
AGE	NEMBUTAL SUPPOSITORY (GRAINS)	AGE	CODEINE SULFATE WITH ATROPINE SULFATE (GRAINS)
To 3 mo	$\frac{1}{2}$	To 1 mo.	$\frac{1}{50}$
4 mo. to 1 yr	1	2 to 3 mo.	$\frac{1}{50}$
1 to 2 yr	$\frac{1}{2}$	4 mo. to 1 yr.	$\frac{1}{50}$
3 to 5 yr.	2	1 to 2 yr.	$\frac{1}{50}$
		3 to 5 yr.	$\frac{1}{50}$

The child is again placed on the toilet for further evacuation just before being given the hypodermic medication. The examination is started when the child is sufficiently drowsy, usually twenty minutes later. Deep anesthesia is unnecessary because of the use of the special examining table to be presently described.

THE POSITION OF THE PATIENT FOR EXAMINATION

Probably the most important single factor for the successful accomplishment of the proctologic examination is the position. If the patient is placed in a comfortable position he will be cooperative and the work of the examiner facilitated. There have been many positions used and recommended. Daniels uses the Sims position with the hips elevated; we find this position limits the view through the proctoscope and that it is difficult. Paulson describes seven different positions, some of which seemed satisfactory to him. He uses mostly a knee-abdomen or chest position, the child being held by an assistant. Santamarina also uses the knee-chest position with a pillow under the hips. The lithotomy position, although comfortable, also limits the height of the view. It has been my experience, after expending considerable effort in the use of previously recommended positions, that all of them are at most times impractical. Because of this, it was decided to develop an examining position which would be applicable to children of all early ages, be comfortable, facilitate the work of the examiner, permit easy introduction of instruments, allow for the best possible views, and release the assistant to help instead of holding the child. The knee-chest or knee-shoulders position would be ideal, as in the adult, but it is just too difficult to keep a child in that strained position with or without anesthesia. However, with the aid of my specially devised table, all the usual obstacles previously encountered have been overcome. The table (Fig. 1) is used for the examination of children from birth to the age of 5 years. Children over 5 years of age are handled as adults, either in the knee-chest position or in the specially devised adult inverted tables.⁵ With the older children a pre-examination dose of elixir of phenobarbital suffices. The occasional difficult child is always a problem and does not affect the established technique.

In Fig. 1 is seen my small, light-weight examining table measuring 25 inches long, 15 inches wide, and 14 inches high.⁶ It is portable, and when not in use is easily stored upon the top of an instrument case. When used, it is placed upon any floor table. The padding is made of comfortable air-foam rubber 2 inches thick. In Fig. 2 a baby is in position for examination. The two straps (X, X) are adjustable to different sized babies and are quickly applied because of the spring snaps (Y, Y). The child, thus strapped, is practically immobile. Also, it is seen that the crossbar (Z) under the pelvis is constructed to lift the abdomen forward and off the table, removing all the pressure on the abdominal wall and also causing the intestines and pelvic viscera to fall forward, thus adding to the ease of the introduction of the examining instrument. When the proctoscope is inserted, there is a suction of air into the bowel which has fallen into the abdomen, creating a negative pressure and thus dilating the walls of

⁶Table manufactured by Shampaine Company, St. Louis, Mo.

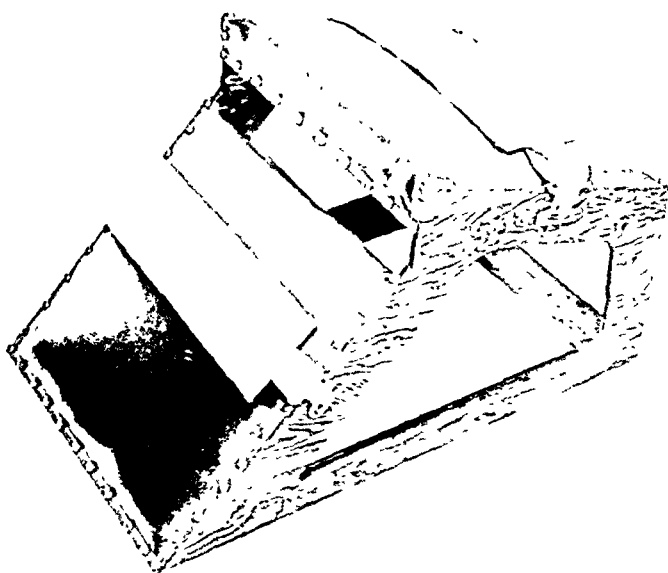


Fig. 1.—The pediatric proctologic examination table.

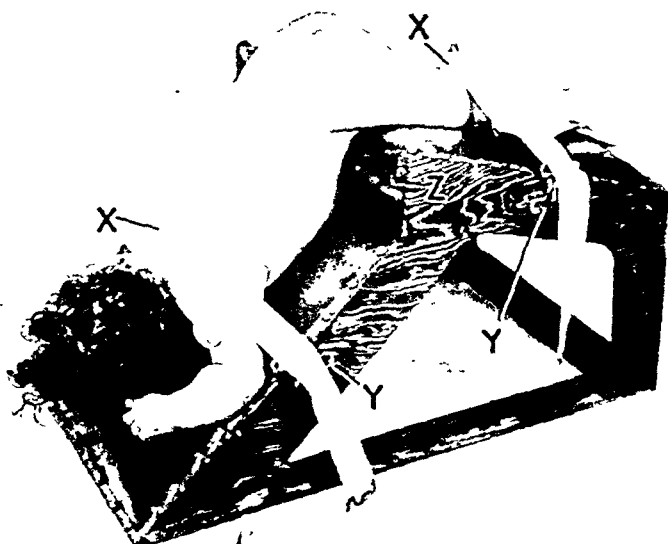


Fig. 2.—An infant in the ideal position for the complete proctologic examination. Note the abdomen in free space.

the bowel for better visualization. An inflating bulb, which is not ever used or recommended, becomes unnecessary. Aside from the proved value during examination, this table has been of inestimable aid during operative procedures, especially the removal of rectal polyps.

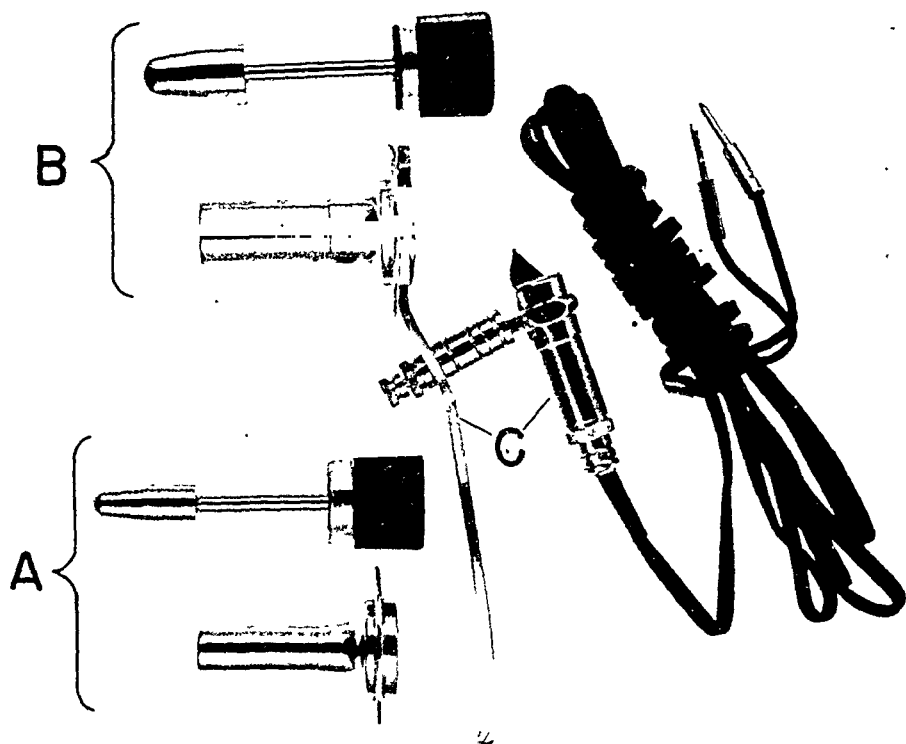


Fig. 3.—The pediatric anoscopes. *A* is the scope used for infants from birth through 3 months of age. *B* is used for infants of 4 months and older. *C* is the universal handle with the attached proximal light.

THE PROCEDURE AND TECHNIQUE OF EXAMINATION AND THE ARMAMENTARIUM

With the patient securely placed in the ideal examining position as shown in Fig. 2, the successive stages in the actual examination can now be safely accomplished in the following order: (A) perianal inspection and palpation, (B) digital examination, (C) anoscopy, and (D) proctosigmoidoscopy.

A. Inspection.—With the perianal, buttocks, and sacrococcygeal areas ideally exposed, observation of any conditions in this region is easily made.

B. Digital Examination.—An immense amount of information can be gained from digital examination through the rectum, not only about the rectum but also about the pelvis and the abdomen. This is not surprising when one realizes the short distance from the anus to the diaphragm in the child. When necessary, further valuable information can be obtained, in the lithotomy position, by bending the child over on himself. The examining finger in the rectum can then be

made to reach a considerable height. In the infant, the anal canal possesses sufficient elasticity and distensibility to permit the introduction of the well-lubricated small finger. In children over one year of age, the index finger will readily enter the anus without doing damage. The full length of the rectum as high as the rectosigmoid can be palpated with ease in the infant and younger child. After inserting the finger its full length, the next maneuver consists of establishing the status of the abdomen and pelvic structures, including the sacrum and coccyx. Next, the tip and volar surface of the examining finger should face the mucous membrane and gradually be withdrawn in a revolving corkscrew fashion all the while hugging the wall. With this approach it should be almost impossible for any gross pathology to escape the finger's touch.

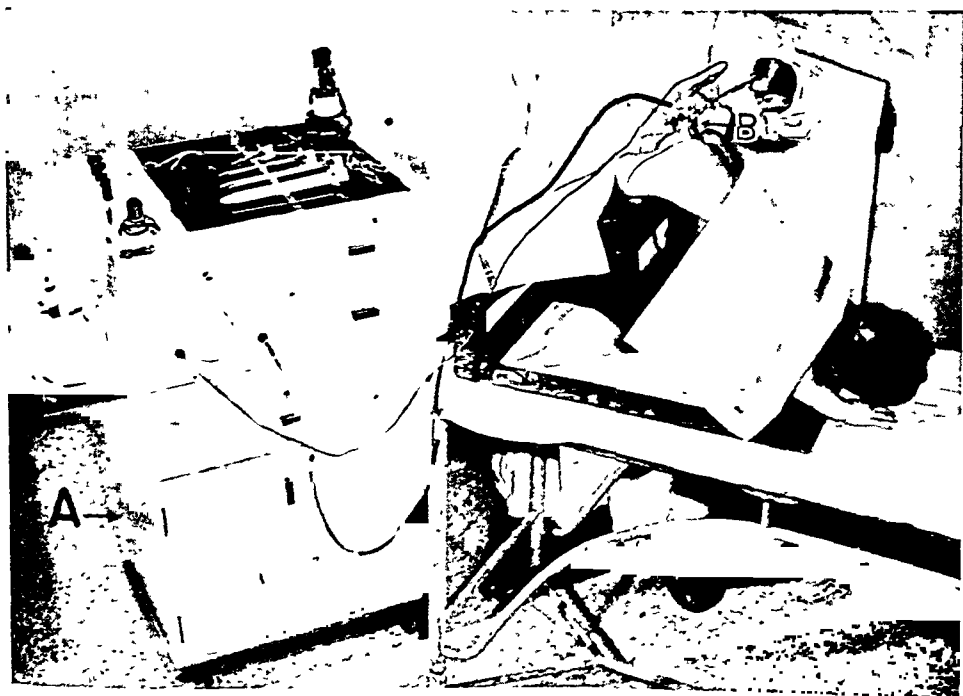


FIG. 4.—The pediatric proctologic examination. An infant in position upon the pediatric proctologic table with a sigmoidoscope (B) in place. The suction tube and light are attached to the author's proctologic diagnostic unit, (A) which is ready for immediate pathologic and bacteriologic studies.⁷

C. Anoscopy.—In the instrumental examination of the terminal bowel I prefer to use the anoscope and rectosigmoidoscope in separate procedures. It has seemed best always to have the examining eye nearest the field of observation. Observing the anal canal and anorectum through the longer proctoscope seemed too distant; also, nonlighted anoscopes seemed inadequate. Accordingly, small, lighted anoscopes (Fig. 3) were constructed in accordance with what was established to be the best dimension⁸ for comfort to the child as well as for the most adequate observations.

Anoscope *A* is $1\frac{1}{2}$ inches long with a diameter of $\frac{1}{2}$ inch (O.D.*) and is used for infants from birth through 3 months of age. Anoscope *B*, used for babies from 4 months through 3 years of age, is $1\frac{1}{2}$ inches long and $\frac{1}{16}$ inch in diameter (O.D.). Adult anoscopes are used for children of 4 years and older. The universal proximal light handle is shown. The need for an attached direct light over any other means of visualization is apparent to those who have tried to examine frightened, squirming children when observations must often be made in split seconds.

The digital examination, which should always precede the anoscopy or sigmoidoscopy, causes the sphincter muscle to relax, thus making easier the introduction of the well-lubricated anoscope. To obtain a still better view, small cotton applicators, 6 inches long, are inserted through the anoscope to flatten out the tissue. The anoscope is gradually withdrawn and all landmarks carefully scrutinized for any pathologic conditions.

D. Proctosigmoidoscopy.—It is when doing the proctosigmoidoscopy that the greatest difficulties have been encountered, thereby discouraging many an examiner. It is only when the patient is placed upon the table herein described, so completely facilitating the examination, that the importance of the proper position is appreciated.

The proctosigmoidoscope of choice is easily passed because of the maintained inverted position (Fig. 2), which causes the intestine to fall into the abdomen. The selection of the rectosigmoidoscopes took into consideration the different lengths and diameters of the rectosigmoid in children of various ages,^{6, 7} and the way to obtain the best possible view with the least amount of discomfort and injury. Furthermore, in deciding upon these rectosigmoidoscopes it seemed necessary to obtain the greatest possible circumference because it was found that the smaller caliber scopes limited the view. Also, as often happened, the mucous membrane crowded into the end of the smaller scopes, thus also reducing the view. So, after using proctoscopes of various diameters and lengths, it became possible to decide upon the use of three sizes as follow†:

1. Newborn infants through 3 months of age— $\frac{1}{2}$ inch wide (O.D.), 6 inches long.
2. 4 months through 3 years of age— $\frac{1}{16}$ inch wide (O.D.) 6 inches long.
3. 4 years and older— $\frac{3}{4}$ inch wide (O.D.), 8 inches long.

In order to have the view nearest the eye, the length of the scopes was limited to the anatomic height for the various ages, using the rectosigmoid as a guide. The proximal light is preferred to the distal light chiefly because in young children the mucous membrane often balloons into the distal end of the scope, thereby obliterating the light and obscuring the view. In addition, in children more than in adults, there is a more frequent overflow of stool, thereby darkening the distal light. The proximal light presents no interference to the view or to the use of applicators, biopsy punches, aspirators, or diathermic appliances.

* (O.D.) indicates outside diameter.

† The anoscopes and sigmoidoscopes were made by National Electric Instrument Co., Elmhurst, N. Y.

TABLE II. FINDINGS IN 547 PEDIATRIC PROCTOLOGIC EXAMINATIONS

FINDINGS		TOTAL NO. CASES
1. Abscess		16
Perianal	10	
Ischiorectal	6	
2. Acrodynia with ulcerative colitis		1
3. Anal ulcer		3
4. Celiac disease		3
5. Colitis		34
Catarrhal	16	
Ulcerative	12	
Dysentery	6	
6. Condylomata acuminata		2
7. Congenital abnormalities		76
Absence of anus with blind rectum	1	
Absence of anus with rectoperineal fistula	2	
Absence of anus with rectovaginal fistula	3	
Absence of anus with rectofourchette fistula	2	
Anorectal stricture	24	
Anorectal membrane, unrelaxed	14	
Imperforate anus	10	
Imperforate anus with anal stricture	1	
Anal band	1	
Spina bifida	17	
Congenital absence of sacrum and coccyx	1	
8. Constipation, chronic		39
With redundant mucous membrane	12	
With anal ulcer, papillitis	1	
With fecal impaction	10	
Uncomplicated	16	
9. Cryptitis		2
10. Diverticulitis		1
11. Fecal impaction		17
12. Fissure in ano		87
13. Fistula in ano		12
14. Foreign body		11
15. Furunculosis		1
16. Hemorrhoids		18
External	7	
Internal	8	
Combined	3	
17. Incomplete rotation of the colon		1
18. Incontinence of feces		1
19. Irritable colon		8
With catarrhal colitis	5	
With spastic colon	2	
With atonic colon	1	
20. Meckel's diverticulum		2
21. Megacolon (all types)		14
22. Negative examinations		27
23. Papillitis, anal		8
24. Parasites		15
Ascaris	1	
Trichuris	1	
Oxyurias vermicularis	13	
25. Pilonidal disease		6
26. Polyps (single)		66
27. Polyposis		6
Acquired	4	
Congenital, familial	1	
With colitis	1	
28. Proctitis		
29. Prolapsus (all types)		6
30. Pruritus ani		65
31. Spastic rectosigmoid with obstruction		4
32. Trauma with ulceration		1
33. Tuberculosis, primary		3
		1

It is safe to introduce the scope up to the rectosigmoid, and with care and patience the pediatrician and general practitioner should be able to master this procedure. The details of introduction of the sigmoidoscope are adequately described elsewhere and need not be repeated here. Most of the proctologic conditions are found in the area up to the rectosigmoid, but when it is necessary to go beyond this level the sigmoidoscopy should be done preferably by the experienced examiner. The tortuous directions of the sigmoid ordinarily make the examination of this region difficult and delicate, but much less so with the approach herein described (Fig. 4). It is best to try to visualize the sigmoid through the sigmoidoscope instead of relying upon the barium x-ray enema because the coiling sigmoid can, on x-ray, reduplicate itself and pathologic change be obscured by the superimposed barium. In particular, polyps in this region can be so obscured. However, the barium x-ray enema becomes necessary for study of the lumen beyond the reach of the sigmoidoscope, especially when the symptoms remain unexplained. It should always be done in the three stages: opaque, evacuation, and contrast.

THE CONDITIONS OBSERVED DURING THE PROCTOLOGIC EXAMINATION

With the routine approach to the proctologic examination as already outlined, it was possible to observe adequately over 500 infants and children, most of whom ranged in age from newborn to 4 or 5 years. In Table II is a summary of the findings.

SUMMARY AND CONCLUSIONS

It was felt that the proctologic examination of infants and children did not receive the attention it deserved chiefly because the examination was difficult and the armamentarium inadequate. For the past ten years an organized study of pediatric proctology has been undertaken. There resulted a satisfactory approach to the examination, which has been detailed in this report. The work of other authors who have previously contributed to the subject has been mentioned. The difficulty in the past has been in preparing the child for a satisfactory and convenient examination. The preparation, sedation, and the position on the new examining table described have overcome this obstacle. The anosopes and sigmoidoscopes described were planned according to anatomic dimensions to give the most complete view. Finally, a summary of the observations of 547 examinations has been listed.

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SOME OF THE PROBLEMS IN THE EDUCATION OF RHEUMATIC CHILDREN

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RHEUMATIC fever is the most prevalent and crippling of all childhood illnesses. It is a dynamic disease which is completely unpredictable in its manifestations, its duration, its multiplicity of explosions, and the extent of wreckage that it may leave behind it. It is not truly a chronic illness but rather an acute protracted disease with long periods of activity interrupted by periods of quiescence.

More recent evidence shows clearly that the rheumatic child during the first few years of his rheumatic history is handicapped by the activity of the disease rather than by cardiac disability resulting from it. It is further clear that the majority of children having quiescent rheumatic fever and minimal cardiac damage may with safety participate in all childhood activity without causing themselves further cardiac damage. Thus, the stigmatizing of a rheumatic child as a cardiac cripple during the quiescent phase of the disease is in the vast majority of cases unwarranted.

A good deal has been written in recent years regarding community organization on behalf of rheumatic fever and rheumatic heart disease.¹⁻¹¹ All these programs speak with great concern about the magnitude of the medical, social, and educational problems involved in the management of this disease. Much has been done in the matter of medical treatment, and a great deal has been learned about the social factors which play an important role in the progress of the disease. It must be admitted, on the other hand, that little attention has been given to the problem of education of rheumatic children. In the past it has been the tendency to stress cardiac damage and the cardiac disability resulting from the damage as the important point of departure in the evolution of any plan for education for children with rheumatic disease. It had been assumed that once a child had rheumatic fever, he must be trained for a life handicapped by cardiac disability. The older thesis was to segregate children with this disease in special cardiac classes to avoid undue exertion and to train them early in the realization that they were handicapped because of their illness. Such thinking is no longer plausible and is certainly not indicated by the recent knowledge of the behavior of this disease. A child is either completely handicapped because of rheumatic activity and cannot attend classes or, in the vast majority of instances, can participate in all childhood activities during the quiescent stage of rheumatic disease.

It is the purpose of this paper to present an analysis of accumulated data gathered from a large children's rheumatic fever clinic. These children were observed over many years. They have been raised under the educational program evolved upon the erroneous concept of the natural history of rheumatic

disease as mentioned above. It is our aim to present some of the problems arising in the course of education of this group of rheumatic children.

MATERIAL AND METHOD OF STUDY

An unselected group of 310 rheumatic boys and girls, 8 to 13 years of age, were studied in the Children's Cardiac Clinic of the Kings County Hospital. A complete medical history and work-up were done in each patient, and a follow-up study was made to ascertain the exact rheumatic and cardiac status. A more detailed medical social history than is usual in a clinic was obtained in each one of these patients. Additional data were gathered from teachers and principals of schools which the children attended. Emphasis was placed upon a detailed study of the school attendance and progress of each child. Many factors were gone into in an attempt to discover the reasons for deviations from the normal expected school progress. Each child and his parents were interviewed on many occasions, and careful note was made of their attitudes toward the illness and particularly toward the child's progress and behavior at school.

The majority of the children did not present any obvious evidence of active rheumatic disease during the entire course of observation. A small group (4.9 per cent) had active rheumatic disease during this same period of observation (see Table I). By far the largest number (94.9 per cent) had normal cardiac reserve, as measured by the usual standards according to the classification of the New York Heart Association. The remainder (5.1 per cent) had depleted cardiac reserve as measured by the same standards. Only an occasional child showed potential cardiac decompensation. (See Table I.)

TABLE I. 310 RHEUMATIC BOYS AND GIRLS 8 TO 13 YEARS OF AGE

	NO. CASES	PER CENT
<i>Rheumatic Status</i>		
Active rheumatic heart disease	15	4.9
Inactive rheumatic heart disease	295	95.1
<i>Cardiac Status</i>		
Classes II and III*	16	5.1
Class I	294	94.9

*New York Heart Association classification

TABLE II. SCHOLASTIC ABILITY

	NO. CASES	PER CENT
In graded classes	301	97.1
Ungraded	9	2.9

The great majority of the total group of children (301 or 97.1 per cent) were known to belong at the level of the average range of scholastic ability: Some were distinctly above average; a small number had low averages; and the bulk showed average scholastic aptitude. None of this group required special "ungraded" instruction. Only nine (2.9 per cent) of the 310 children studied were distinctly below average and had to be placed in ungraded classes. (See Table II.)

This study, therefore, deals with a group of rheumatic boys and girls most of whom presented no evidence of active rheumatic disease. had good cardiac reserve, and showed normal scholastic ability.

RESULTS

Of the total group of 310 children, 161 (53.3 per cent) were behind in their grade status at school* (Table III). In this group, it was found that the greatest number of terms lost through illness was ten and the smallest number of terms was one. The average for the entire group was 2.8 terms. This would bring the age of graduation of this group up to close to 17 years. Only 46.7 per cent of the total group were found to be in the proper grade according to age. These apparently had not lost time through illness. The marked discrepancy in age between the two groups of children resulted from loss of time due to illness in the first and larger group rather than from lack of scholastic ability.

TABLE III. SCHOLASTIC STANDING

	NO. CASES	PER CENT
In the proper grade according to age	140	46.7
Behind their age-grade	161	53.3

It became clear early in the study that this marked age difference presented many problems in school adjustment. Table IV demonstrates that only about two-fifths (40 per cent) of the children seemed to be well adjusted to school and that one-third (34.3 per cent) were so ill adjusted to their school program that they either interrupted their studies completely or became serious behavior problems at school and at home. Inquiry into the reasons for maladjustment brings out forcibly the fact that those children who quit school before graduation do so primarily because of the discrepancy of age and grade rather than because of low scholastic ability. In a good many instances discrepancy in body size was sufficient to cause acute embarrassment leading to severe emotional disturbance. In other instances, physical and intellectual maturity in the older children when compared to their classmates led to acute confusion and was responsible for the creation of an attitude of futility in regard to continuation of school. It is noteworthy that only a small percentage (12.9 per cent) were poorly adjusted in school as a direct result of severe illness and prolonged rheumatic activity (Table IV).

TABLE IV. SCHOOL ADJUSTMENT

	NO. CASES	PER CENT
Schooling interrupted (quit school before graduation)	25	8.1
Severe behavior problems (continuation in school problematic)	26	8.4
Moderate problems (in urgent need of guidance)	55	17.8
Need minor adjustments	42	13.5
No problems	122	39.1
Ungraded, very sick children with active cases	40	12.9

COMMENT

The chronicity and unpredictable behavior of rheumatic disease in children presents many complex medical, psychologic, and social problems. Solid

*The average child enters public school in the City of New York at 6 and graduates at 14.

progress has been made in recent years in the clinical behavior and therapeutic management of this disease. A good deal of headway has been made in the study of the social aspects of rheumatic fever. The emotional problems arising from the nature of this disease, however, have received little consideration. The education of the parent and the patient is only in the blueprint stage of any full-scale communal planning for the management of rheumatic disease in children. Little thought has been given to the need for adequate schooling for this group of children, and it is obvious that inadequate and poorly planned education for large groups of children who "need education more, not less, than healthy children,"¹² results in the creation of large numbers of maladjusted citizens who present burdensome problems to their immediate environment, to clinics, hospitals, and social service agencies. Under our present ill-conceived plan of education, rheumatic children attend classes in which their classmates are from one to five years younger. Their chronologically equal playmates are much advanced in school. The youngsters realize that postponement of graduation from the elementary school to the age of 17 makes a high school education well-nigh impossible. This realization leads to a sense of futility and breeds discontent.

There are, at the present time, no accurate figures upon which to base the estimate of the magnitude of this problem in the City of New York. It is estimated that from two to four children per hundred have rheumatic disease. On the basis of our experience, fully one-half of this group of children are profoundly traumatized by the inadequate plan for their education. Roughly, therefore, from 10,000 to 20,000 children in the City of New York are brought up under a plan of education which inevitably leads to the existing maladjustment problems in school and, in the future, to the more difficult problems in rehabilitation.

On the basis of our experience it would seem reasonable, from the medical standpoint, to admit children with rheumatic heart disease to regular classes and not to stigmatize them as cardiacs by limiting their physical activities. Long-term experience shows that children with minimal cardiac damage (and these constitute the majority of rheumatic children) can and should be permitted to participate in all the normal physical activities of childhood. It is further suggested that those rheumatic children who have missed a good deal of schooling because of acute illness should be given adequate bedside teaching during the acute illness and should be returned to school to a grade commensurate with the age of the child. In addition, it might be a wise policy to permit a rheumatic child with average intelligence and ability to be transferred to vocational high school upon the attainment of the age of 14 years rather than to hope that he might be willing to enter such a school at the age of 17 upon his graduation.

SUMMARY

1. The problem of education of rheumatic children has been studied in an unselected group of 310 children at the Children's Cardiac Clinic at Kings County Hospital.

2. Nine out of every ten children in the group were found to have quiescent rheumatic disease and average scholastic ability.
3. More than half of the group were found to attend grades below their age level.
4. Three out of every five children in the group presented various problems of maladjustment and, in some instances, severe behavior problems resulting from inadequate regard to the education of this group of children.

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Case Reports

ALKALIGENES FECALIS BACTEREMIA AND MENINGITIS

REPORT OF TWO CASES IN NEWBORN INFANTS

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IN REVIEWING the literature, one is impressed by the variety of organisms which have caused meningitis. Some of these are considered to be harmless nonpathogens, while others are known to be potentially invasive. Many cases of meningitis are reported in the literature which are due to gram-positive or negative bacteria. Some are caused by viral agents, a few claim their etiology in yeasts and molds, and still fewer are caused by metazoan parasites (e.g., *Cysticereus*).

A review of the literature reveals that, to date, only six cases of meningitis due to organisms of the genus *Alkaligenes* have been reported. The first case caused by an organism of this genus was reported by Gatewood¹ in 1931. In 1934, Mason² successfully treated a 12-year-old child with *A. fecalis* meningitis by repeated cisternal punctures. In the same year Spray and Hawk³ reported the disease following otitis media. Kutscher⁴ in 1937 reported on a similar case caused by *A. bookeri* and reviewed the literature on gram-negative *Bacillus meningitides*. In 1942 Voorhies and Wilen⁵ reported their case of *A. fecalis* bacteremia and meningitis. The most recent report of a case of this sort, occurring in a 42-year-old seaman, was made by Terry, McBane, and Dean⁶ in 1947.

The following two cases of *A. fecalis* bacteremia and meningitis are believed to be the first reported in newborn infants.

Both of these children were born in the same hospital and were transferred to the Children's Hospital when it became evident that their respective illnesses were of a grave nature. One of these children was Negro, the other white. They were delivered in different delivery rooms by different doctors, and taken care of in separate nurseries by different nursing staffs.

No definite epidemiologic chain was ever established between the two cases, even though the children were born in the same hospital within two days of each other.

CASE REPORTS

CASE 1.—B. B. W., a 4-day-old white male infant, was delivered after a prolonged second stage of labor (three hours) requiring forceps. No other maternal history was available. The birth weight was 6 pounds, 4 ounces (2,840 Gm.). Persistent mild cyanosis and crying were noted after birth. Fever appeared on the second day of life, and persisted and reached a peak of 102° F. on the fourth and last day. The baby became jaundiced on the third day of life. The following day his condition was so poor that he was given clyses and penicillin. When there was no apparent improvement he was transferred to the Children's Hospital, where he was found to be jaundiced and cyanotic. He did not cry. Respirations were irregular with changes in the breath sounds. A

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The bacteriologic examinations were made by Miss Mary Jane Pistorius, M.T.

full fontanel was noted. The infant expired during a plasma infusion within an hour after his arrival. Laboratory work on the last day of life revealed hemoglobin 15.0 Gm., erythrocytes 4.6 million, leucocytes 12,500, neutrophils 53 per cent, lymphocytes 43 per cent, and monocytes 4 per cent. Urinalysis was positive for albumin and sugar. The specimen was loaded with clumped leucocytes and granular and hyaline casts.

Necropsy Findings.—The body was that of a fairly well-developed and nourished white male infant. The cord stump and tie were still attached. The stump was black but not grossly infected. Five cubic centimeters of xanthochromic fluid were obtained by cisternal tap. Examination of this fluid revealed: 750 leucocytes per cubic millimeter with 78 per cent polymorphonuclear leucocytes and 22 per cent lymphocytes; approximately 800 mg. per cent protein; and less than 20 mg. per cent sugar. Gram-negative bacilli were seen on direct smear.

The superficial vessels of the brain were congested, but there was no gross hemorrhage. Scattered over the surface of the brain and particularly between the gyri and along the superficial blood vessels there was a thin whitish and yellowish exudate which was most prominent over the cortex and least over the base. The ventricles contained no hemorrhage or exudate.

Anatomically the remainder of the post-mortem revealed nothing significant. A circumcision had not been performed. There were small quantities of fluid in both pleural cavities and in the peritoneal cavity. The organisms present in spinal fluid ante mortem and in the post-mortem specimens of cisternal fluid, heart blood, urine, splenic fluid, and pericardial fluid, all gave the reactions shown in Table I.

TABLE I

GRAM STAIN	MOTILITY	LAQUEY'S GLUTIN	INDOLE	VOGES- PROSKAUER	METHYL RED	DEXTROSE	SUCROSE	LACTOSE	MALTOSE	MANNITE	LITMUS MUC
-	-	-	-	-	-	-	-	-	-	-	Sl. alk.*
Conclusion: <i>A. fecalis</i>											

*Sl. alk.—slowly became alkaline.

CASE 2.—B. B. H., a 6-day-old Negro male infant, was delivered at term without difficulty. No additional maternal history was available. A circumcision was done on the fourth day of life. The following day the infant had a temperature of 102° F. On the sixth day of life his condition became critical, and he was noted to have a temperature of 104° F., convulsions, cyanosis, nuchal rigidity, and a bulging fontanel. He was started on penicillin intramuscularly. Later in the day he was transferred to the Children's Hospital.

Spinal puncture on admission was productive of xanthochromic to bloody fluid containing 1,400 leucocytes (27 per cent polymorphonuclear leucocytes, 65 per cent lymphocytes, and 8 per cent endothelial cells), and 600 mg. per cent protein. The baby was given intramuscular and intracisternal penicillin and oral and subcutaneous sulfadiazine.

In spite of all therapeutic and supportive therapy the child pursued a downhill course and died fifteen hours after admission.

Necropsy Findings.—The body was that of a poorly nourished and developed, light-skinned, Negro male infant. The umbilical stump was still attached, was firm and black and free of gross infection. The glans penis was swollen, dark red in color, and appeared to be gangrenous. There was no evidence, however, of any direct spread of infection from the penis into the abdominal cavity.

Bloody fluid was withdrawn from the cisterna magna. A direct smear of this fluid revealed the presence of gram-negative bacilli.

The meningeal and pial vessels of the brain were engorged. There was a fresh hemorrhage in the infratentorial region, more marked on the right. Covering the surface of the brain, most marked over the convex surface and between the gyri, was a light yellow-green exudate. The ventricular system and the choroid plexuses were normal. A small blood clot was observed in the fourth ventricle.

The lungs were heavy but crepitant and floated in water. Frothy clear fluid could be expressed by pressure on the lung parenchyma. The pericardial sac contained 10 c.c. of dark yellow fluid. The epicardial surface, especially over the auricles, and the great vessels were speckled with a yellowish exudate.

The peritoneal cavity contained 30 to 40 c.c. of dark yellow fluid. Filmy adhesions were present between the visceral peritoneum and the anterior abdominal wall. A light yellowish exudate was present, scattered over the intestines and the spleen. The organisms present in cisternal fluid, pleural fluid, peritoneal fluid, heart blood, and urine, all gave similar reactions, as seen in Table II.

TABLE II

GRAM STAIN	MOTILITY	LIQUEFY GELATIN	INDOLE	VOGES- PROSKAUER	METHYL RED	DEXTROSE	SUCROSE	LACTOSE	MALTOSE	MANNITE	LITMUS MILK
-	+	-	-	-	-	-	-	-	-	-	Sl. alk.*
Conclusion: <i>A. fecalis</i>											

*Sl. alk—slowly became alkaline.

DISCUSSION

According to Topley and Wilson,⁷ *A. fecalis*, originally named *Bacterium fecalis alkaligenes*, was isolated from human feces by Petrushky in 1896. Although usually a harmless saprophyte in the intestinal tract of man, this organism may occasionally give rise to infections of the enteric type. Mason² quotes other authors as describing the general picture of typhoid fever being caused by *A. fecalis*.

The organisms present in the various fluids collected from these two children were identified according to Bergey's Manual.⁸ There was complete agreement of bacteriologic evidence in all instances. The results of these bacteriologic determinations have been summarized in Tables I and II.

SUMMARY

Two additional cases of bacteremia and meningitis due to *A. fecalis* are added to the literature. This brings the total to eight.

The two cases reported are the first of bacteremia and meningitis caused by *A. fecalis* in the newborn infant.

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TETANUS NEONATORUM

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SUMTER, S. C.

AMONG the most serious infections of the newborn infant is tetanus neonatorum. The mortality rate varies in different reports from 50 to 98 per cent. We feel that with the use of penicillin together with antitoxin and sedation the mortality rate may be reduced.

CASE REPORT

M. A. F. was delivered on June 13, 1947, by a midwife. The delivery was full term, spontaneous, and the mother's serology was negative. The child breathed without difficulty. At the birth the midwife placed a "clean patch" on the umbilicus. The child appeared well, ate well, and showed no sign of any difficulty until June 17, four days after birth, and was admitted to the hospital on June 21.

On admission the physical examination revealed a well-developed and well-nourished female Negro infant, very acutely ill, with temperature of 99.6° F. The infant was very rigid and would go into a state of marked tonus with any stimulation. The skin was warm and dry. The facies showed: lips pouching, jaws stiff, trismus, rigidity, and marked retraction. The eyes were tightly closed, and the ears and nose were negative. The throat was not well visualized due to rigidity of the muscles of the mandible. The lungs were clear to auscultation and percussion. The heart rate was normal. There was no arrhythmia, and the sounds were of good quality. The abdominal muscles were rigid, and no masses or tenderness were present. The umbilicus was protuberant, one plus inflamed, and there was a serosanguineous exudate present. There was no odor of the umbilicus. The genitals were those of a normal newborn female infant. The extremities were extended and stiff. The reflexes could not be determined because of the stiffness present.

The child on admission was given 80,000 units of tetanus antitoxin, 60,000 units intramuscularly and 20,000 units about the umbilicus. In addition, she was given $\frac{1}{8}$ gr. of sodium phenobarbital every forty-five minutes until relaxation occurred. A total of $1\frac{1}{8}$ gr. was administered before relaxation occurred. No respiratory distress developed. In order not to stimulate the child, she was watched closely for dehydration and no feedings were given and no fluids given parenterally except when dehydration threatened.

She was premedicated with $\frac{1}{800}$ gr. of atropine and carried to the operating room the morning of June 22 (ten hours after admission). The umbilicus was excised, and the following notes were made of the operation: Under ether anesthesia the abdomen was cleaned and draped as a sterile field. The umbilicus was followed for a depth of about $\frac{1}{4}$ inch through the fascia, and as it was gradually excised at this depth with clamps being applied, it was noted that there was a thrombosis in all the vessels that were encountered. A small portion of the surrounding fascia was removed and all areolar tissue in this area that could be removed was taken out. After the stump of the umbilicus had been thoroughly secured with clamps the umbilicus and deeper structures were excised. As they were cut off the omphalomesenteric veins and arteries could be visualized. They were partially open but were mostly thrombosed. These vessels were thoroughly secured with No. 1 chromic catgut ties. Following this a small catheter was inserted beneath the fascia, and the fascia was closed loosely about the catheter with two interrupted No. 24 cotton sutures. The skin and

subcutaneous tissues down to the fascia were left wide open and a petroleum jelly gauze dressing and a bandage for the outside were applied, the catheter being brought through the bandage. Following this the patient was returned to the ward in relatively good condition. During the operation the patient's condition appeared fairly good. There were no convulsive seizures during the operation.

Culture of the umbilicus revealed *Staphylococcus albus*, gram-negative bacilli and gram-positive bacilli.

On return from the operating room the infant was given 30,000 units of penicillin every two hours, $\frac{1}{2}$ gr. phenobarbital every four hours, and 100 c.c. of 2½ per cent glucose in distilled water subcutaneously, immediately. In addition, the tube in the umbilical area was irrigated with hydrogen peroxide every hour. Owing to the fact that it was difficult to determine if the entire infected area had been removed, 5,000 units of tetanus antitoxin were given every eight hours.

At 11 P.M., the day of the operation, she became more rigid, and the phenobarbital was increased to $\frac{1}{4}$ gr. every other dose.

Fluids were maintained by the subcutaneous route, with 2½ per cent glucose either in distilled water or in normal saline.

She remained moderately relaxed with normal respiration until the second postoperative day (June 24), at which time her respirations became shallow and slow. She was given 0.5 c.c. of coramine, given oxygen, and placed in an incubator. The incubator was used to facilitate the giving of the oxygen and to maintain the body temperature, which was regulated with some difficulty due to the shortage of nursing care. The sedation was discontinued due to the respiratory depression.

In addition to the fluids given, 60 c.c. of plasma were given intravenously. Sips of glucose and formula every two hours were begun.

On June 25 the rigidity began to return and phenobarbital, $\frac{1}{4}$ gr., was again given and continued every four hours in $\frac{1}{8}$ gr. doses.

On June 26 the antitoxin was reduced from every eight hours to once daily with the same dosage, and the phenobarbital, $\frac{1}{8}$ gr., was given every eight hours. The relaxation was maintained.

On June 28 tetanus antitoxin was discontinued. July 1, 60 c.c. of plasma were given intravenously. The following day, oxygen was changed to p.r.n. and sedation was discontinued. On July 3 penicillin was reduced to 20,000 units every three hours. Phenobarbital had to be resumed on that day because of the return of rigidity. However two days later the phenobarbital was discontinued.

On July 6 the formula was increased. The child was much improved and ate well.

On July 10 cod liver oil and orange juice were begun. Penicillin was discontinued on that date.

On July 21 the child was discharged, in good condition.

COMMENT

Tetanus neonatorum is easily diagnosed because of the typical history and symptomatology. A positive culture of *Clostridium tetani* may not be obtained in many cases, but this is not necessary for diagnosis. The conditions that may simulate tetanus and must be differentiated are birth injuries, infectious meningitis, and tetany.

The mortality rate has been reduced as follows: 1921 through 1928, 66 per cent; 1929 through 1935, 55 per cent; 1936 through 1946, 28 per cent.²

The use of penicillin in doses of 30,000 units every three hours appears to be adequate and should prove a valuable adjunct to the therapy. We feel that

due to the difficulty of determining if all of the infected area has been removed, the antitoxin should be given in frequent doses to maintain a good titer. As to sedatives, phenobarbital was given instead of Avertin, magnesium sulfate, or other types. This drug was chosen in order to obtain a more smooth, continuous, sedative effect. This smooth sedation prevents laryngeal spasm and other signs of irregular relaxation that may occur in shorter-acting drugs. This is particularly important at times when hospitals are short of all types of help.

SUMMARY

A case of umbilical tetanus with recovery is reported. Therapy with penicillin, repeated administration of tetanus antitoxin, and small frequent doses of sodium phenobarbital is described in conjunction with excision of the lesion.

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LACK OF CORRELATION BETWEEN POSSIBLE Rh INCOMPATIBILITY AND MONGOLIAN IDIOCY

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THE following case history seems worth reporting because a Mongolian idiot was the only living offspring of an Rh-positive father and an Rh-negative mother.

CASE REPORT

J. R. J. was admitted to the Feeble-minded Division of the Crownsville State Hospital on April 1, 1942. He was born Nov. 17, 1936, of Negro parents. Pregnancy and delivery were uneventful. The patient was the first child of this couple. His birth was not preceded but followed by "several" miscarriages and stillbirths. (The exact number is not known.) No other living child was born to the parents later on. The father, who occupied a leading position in the Negro youth movement, got "easily nervous" and stammered. The mother rejected the child as soon as it became clear that no mental improvement was to be expected and withdrew entirely from him.

The patient was a stout, short, typical Mongolian idiot. At the age of 11 years his height was 42¾ inches (average of normal children, 53 inches), and his weight was 52 pounds (average, 73 pounds). He gave the impression of a stout 5-year-old boy. All carpal bone centers were well developed. He had an epicanthus, mongoloid eyes, an extreme hypotony, a high vaulted palate, but no cleft palate. There was no congenital heart malformation, but there was a congenital cataract on both eyes. The distance between the big toe and the other toes was not significantly increased. There was no Mongolian spot on the back. The patient's Wassermann reaction was negative. The boy was of very low mental endowment and unable to produce more than some hoarse, barking noises. He hit himself constantly with his fists against his temple. He was without any contact with his environment. The previous winter, for an unknown reason, he had suddenly lost weight to a point that could be called critical. After a few weeks, again without any apparent reason, he picked up weight and was in good physical condition at the time of examination.

Because of the appeal of Dr. Theodore H. Ingalls,² of Boston, to try to collect cases in which insignificant intercurrent infections during pregnancy might have been responsible for the appearance of Mongolian idiocy, we questioned the patient's parents. There had been no intercurrent infection during pregnancy which could be related to the patient's condition.

The problem of Rh incompatibility had been discussed with the parents before and had in the meantime taken root in their minds. Their case was studied in the Baltimore Rh-Typing Laboratory, and I am indebted to the director, Dr. Milton S. Sacks, for making available his data to me. It was found that the patient's father was Rh positive and the patient's mother, Rh negative, but her serum failed to show evidence of Rh or Hr immunization. The patient's blood-group study revealed him to be Group A₁ MN Rh₂ (positive).

Because no sensitization could be shown in the mother's serum there seemed to be little reason to connect either the stillbirths and miscarriages or the birth of a Mongolian idiot with the difference in Rh groups in both parents.

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COMMENT

This case is reported because it seems important to record the simultaneous occurrence of different Rh groups in the parents and a Mongolian idiot as the only living offspring. If enough cases can be assembled it might be possible to determine mathematically whether or not this coincidence is more than a chance.^{5, 10}

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Medical Care

TREATMENT OF COMMON SKIN DISEASES IN INFANTS AND CHILDREN

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IN THE treatment of skin diseases as in so many other fields, recent years have seen many changes, not a few of which have been brought about by experiences gained in World War II. The most notable advances have been made in the parasitic and bacterial infections. Even though the practical testing of new methods of treatment was accomplished chiefly in adults, they have been demonstrated to apply equally to children.

In dealing with skin diseases in children, it must always be remembered that we are confronted with an immature organ, which is more sensitive to both endo- and exogenous noxae than is the adult skin. The skin, like other organs in the child, has had no opportunity to become desensitized to either internal or external toxins or bacteria, and is for this reason more susceptible to disease.

Many skin diseases are peculiar to children, or, at least, occur in children so much more frequently than in adults as to be recognized as chiefly pediatric problems. Among the most frequent skin diseases in children, and comprising some 80 per cent of these, may be mentioned eczema, scabies, pediculosis capitis, fungous infections such as tinea capitis, tinea corporis, and dermatophytosis of the feet, bacterial infections (impetigo, etc.), dermatitis venenata, miliaria, intertrigo and napkin dermatitis, verrucae, urticaria papulosa, angioma, and vitamin deficiencies. Wright,¹ in his compilation of skin diseases encountered most frequently in practice, found these conditions accounting for 60 to 75 per cent of cases.

ECZEMA

This term, although not very specific, is still used for want of a better one. The infantile group of eczemas is divided into the allergic or atopic, and idiopathic or simple types. The other types, such as contact, seborrheic, drug, or physical eczema, are more amenable to treatment. Quite recently a disturbance in the metabolism of essential fatty acids has been suggested as a possible etiological factor in some forms of eczema. Having observed an improvement in 65 per cent of patients following an addition of 30 to 60 Gm. of lard (which contains abundant unsaturated fatty acids) daily for two to three months, Hansen and his associates² concluded that the administration of fats rich in unsaturated fatty acids will bring improvement even though other therapeutic methods are withheld.

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The importance of relieving itching by topical applications, sedation, and splinting must be emphasized. A most careful anamnesis is required to disclose the origin of sensitization or the offending contact substance, since its elimination forms an important step in obtaining a cure. The introduction of the patch test for detection of the offending substance, and of new foods to be substituted for those causing allergic reactions, have considerably simplified the management of allergic children. Various superfatted and detergent soaps have been introduced for cleansing purposes. Dietary faults must be corrected. Proper rest, fresh air, and exercise are important. Bowel elimination must be regulated.

For topical medication in the acute stage, aluminum acetate solution, diluted 1 to 20, or saturated solution of boric acid, or calamine lotion may be used. In the more chronic stages, tars, ichthyol, salicylic acid, or, if infection is present, ammoniated mercury (1 to 2 per cent) or mild mercurous chloride (2 to 5 per cent) in an ointment have been found useful. Roentgenotherapy should not be employed in the treatment of eczema because the good results thus obtained are only temporary.

URTICARIA PAPULOSA

This condition is known also as lichen urticatus or prurigo simplex. The eruption appears on the extremities, face, and buttocks (Fig. 1), and consists of lesions with a tiny central papule surmounted by a vesicle, red in color and intensely pruritic. It occurs between the ages of 2 and 8 years, and may persist for years. Attacks are frequently seasonal, and many children have atopic histories.³ Skin testing is of no value for diagnosis or treatment of this condition. Treatment consists of reducing the carbohydrates in the diet, the application of antipruritic lotions, the intramuscular injection of parathormone extract, 25 units twice weekly, and administration of calcium lactate or gluconate, 1.0 Gm. three times daily.

PEDICULOSIS CAPITIS

It is encouraging to report that great progress has been made in the management of this nuisance, especially as a result of the intensive study of the prevention of louse-borne diseases in the recent war.⁴⁻⁶ The experiences thus gained have led to greater simplicity and efficiency in the treatment of this condition.

In clinic practice, the application of equal parts of kerosene and olive or other vegetable oil, rubbed into the scalp and allowed to remain overnight, followed by a shampoo and fine-tooth combing, remains the standard treatment. This method is effective and economical. The treatment should be repeated in three days.

A newer method consists in the application of DDT, in the form of a powder or a solution. Other efficacious preparations have recently appeared. Excellent results have been obtained by application of a solution containing DDT, 2 per cent, naphtha, 15 per cent, emulsifying agent, 5 per cent, and water, 78

per cent.⁷ This is applied to the scalp and hair with a paint brush, and the solution is washed out after twenty-four hours, when the ova may be removed with a fine-toothed comb. This treatment has proved successful in all cases, and there have been no signs of irritating effects or toxic reactions. DDT should not be left in contact with the skin for long periods of time, and the eyes should be carefully protected, nor should the solution be applied in the presence of skin lesions.



Fig. 1.—Papular urticaria with lesions on face, arms, and legs. Note absence of lesions on body.

DDT powder⁸ has also yielded good results. This contains one part of DDT to nine parts of inert talcum powder. Following its application, a towel is wrapped about the child's head, and by next morning, the ova can be easily removed with a fine comb. Should any ova remain, a second or even a third application, at intervals of one week, may be employed. No recurrences have followed such treatment. A 25 per cent benzyl benzoate emulsion has likewise yielded good results. The scalp is shampooed, dried, and the emulsion applied and allowed to remain for twenty-four hours. The scalp is then shampooed again, and a fine-toothed comb is used. The hair is then thoroughly brushed.

Still another very recent method of treatment for head lice is the application of a solution containing 5 per cent isobornyl thiocynoacetate and 0.6 per cent dioctyl sodium sulfosuccinate (Bornex). One or two ounces of the solution is worked into a lather, applied to the hair, and left in place for five to ten minutes. The hair is then combed with a fine comb and dried, and is shampooed on the following morning. In rare cases, a second application may be needed.

This solution is recommended because it has a pleasant odor and does not stain. In a large series of clinic cases, I have found it very effective, and it has produced no side effects or contact dermatitis.

It is necessary to be on guard for possible dermatitis due to any of the previously mentioned drugs as they all have sensitizing potentialities in susceptible individuals.



Fig. 2.—Scabies, showing impetiginized lesions on scalp, neck, and body.

SCABIES

This infestation with the *Sarcoptes* or *Acarus scabiei*, is seen most frequently in clinics where the patients come from the lower economic or social strata. In children, the lesions become more impetiginized, and may be found on the face, scalp (Fig. 2), hands, and feet, as well as the other usual sites.

Although many new methods of treatment have recently been advocated and have been found satisfactory, for the average clinic patient sulfur ointment remains the standard treatment. If secondary infection is not too severe, a 2 to 3 per cent precipitated sulfur ointment is recommended for infants and small children, and a similar 5 to 8 per cent ointment in older children. Mild impetiginization is not a barrier to the use of sulfur. A written instruction sheet should be given to the patient. After a hot bath, the ointment is applied to the entire cutaneous surface, and the face, scalp, hands, and feet thoroughly

anointed if infected. This treatment is repeated morning and night for four days. The same underwear and bed linen is used, and no bathing is permitted during this period. Another hot bath is then taken, and fresh underwear and bed linen, which have previously been boiled, are used. If the itching still continues after this period, it may be due to a sulfur dermatitis or to persistence of the infection.

Benzyl benzoate emulsion (25 per cent) is a rapid and clean method, but about 10 per cent of patients subjected to this treatment have developed a dermatitis. After a hot bath, the emulsion is applied, allowed to dry, and reapplied. Twenty-four hours later, the patient bathes again, and the emulsion is applied as on the previous day. Fresh sterilized underclothes and bed linen are used.

Another preparation which has been found effective consists of benzyl benzoate (for mites and nymphs), 10 parts; DDT (for larvae), 1 part; benzocaine (for ova), 2 parts; Tween 80,* 2 parts; and water to make 100 parts. The method of application is the same as for benzyl benzoate.

Recently, Goldberg⁹ has reported 95 per cent cures and no irritation from application of DDT 7.0 Gm., xylol, ether, and liquid petrolatum, of each equal parts, to make 100.0. This is applied in the same manner as sulfur ointment.

One of the most recent drugs, which has yielded excellent results, is one per cent of the gamma isomer of 1,2,3,4,5,6 hexachlorocyclohexane, in a vanishing cream base (Kwell). This preparation is nongreasy, nonstaining, and odorless. I have not to date seen any irritation from its use, and consider it safe for the treatment of children. It is applied nightly for three nights, with care to protect the clothing and bed linen. This ointment can be used also when infection is present.

FUNGOUS DISEASES

Tinea Capitis.—Ringworm of the scalp (Fig. 3) is still prevalent among school children. It occurs only occasionally in infants and adults. In the Philadelphia area, about 95 per cent of cases have been due to the *Microsporon audouini* (human type). The next in point of frequency is the *Microsporon lanosum* or *canis* (animal type). The latter type responds readily to any of the fungicides.

In the human type of ringworm, in children, x-ray epilation^{10, 11} remains the most effective and standard treatment. Toward puberty, there is a tendency to spontaneous cure. Recent experimental studies have shown that after puberty the sebaceous glands of the scalp secrete a sebum which contains, in higher concentration than before, low-boiling saturated fatty acids, with selective fungistatic and fungicidal action.

A concentrated effort is being made to control the present epidemic in this area.¹² The barber shops constitute the greatest source of dissemination. I have advised all parents to provide their own personal clippers, comb, and

*Atlas Powder Co., Wilmington, Del.

scissors, and request the barber to use them instead of his own. By so doing infection may be avoided.

Schools should be equipped with Wood's light for the diagnosis of ringworm. It is unnecessary to forbid an infected child to attend school, but all infected children should be required to wear a skull cap, which should be boiled daily.

Before resorting to x-ray therapy, a trial with local medication for a period of at least two months is justifiable. Our proportion of cures with local medication has ranged from 10 to 25 per cent. It is my impression that the greatest number of cures has been effected with salicylanilide, 5 per cent, in Carbowax 1500, or, when this fails, with copper undecylenate, saturated solution in Carbowax 1500, or copper undecylenate, 10 per cent, in an isopropyl alcohol vehicle (Decupryl). The medication is applied twice daily with friction to the af-



Fig. 3.—Tinea capitis due to *M. audouini*. Defluvium and circinate appearance are characteristic.

Fig. 4.—Permanent alopecia following tinea capitis. Parents treated child with home remedies.

ected areas for ten minutes. Sixty to eighty applications may be required for a cure. If a cure is not obtained in this time, then x-ray therapy should be instituted.

X-rays do not kill the fungus, its curative effect being due to the resulting epilation. There need be no fear of permanent alopecia if the roentgenotherapy is applied under competent and experienced supervision, as demonstrated by thousands of epilations with no ill effects, performed all over the world. On the other hand, I have seen patients develop permanent alopecia when left untreated or made the victims of home remedies (Fig. 4).

Tinea Corporis.—This is usually caused by the *M. lanosum (canis)*, which is of animal origin. The most frequent sites of infection are the exposed areas of the body, the face (Fig. 5) and arms. The lesions are easily cured by the application of tincture of iodine, one-half strength, or 5 per cent ammoniated

mercury ointment, or 5 per cent sulfur ointment, or salicylic acid, 3 per cent, and benzoic acid, 6 per cent, in hydrophilic ointment. Each is applied several times daily for two days.

Dermatophytosis of the Feet.—This condition is seen less frequently in children than in adults. The remedies now on the market are legion, and a word of caution is not out of place, since use of the wrong remedy or too strong a preparation or even too many applications of the right remedy may lead to serious allergic reactions and complications.¹³⁻¹⁴ In the acute phase, foot baths in saturated solution of boric acid or potassium permanganate, 1:10,000, will relieve the inflammation. In the subacute stage, the newer fatty acids, such as propionic acid and undecylenic acid,¹⁵ are used. Whitfield's ointment, one-half strength, is popular but inefficient, and is used for its exfoliative effects. Shoes and white socks must be disinfected and changed frequently.¹⁶



Fig. 5.—*Tinea corporis (circinata)* contracted from a dog.

BACTERIAL INFECTIONS

Bacterial infections constitute a large percentage of the dermatoses seen in children. They may be primary infections, such as impetigo or ecthyma, or secondary, such as infectious eczematoid dermatitis, eczema, dermatophytosis, and infected scabies. The treatment of the secondary infections must be directed toward the original disease. We are here chiefly concerned with the primary infections, in which the most common bacteria encountered are hemolytic *Staphylococcus aureus* and beta hemolytic streptococci (ordinarily Lancefield, Group A).

Before local medication is applied, the crusts and debris must be removed so that the medication may reach the bacteria. This is accomplished either with mineral oil or warm boric acid compresses or a starch poultice. The latter is prepared as follows: Mix two tablespoonfuls of wheat starch and one teaspoonful of boric acid crystals into a cream with cold water. Add to this cream a pint of boiling water, and stir. One teaspoonful of glycerin may be added

to prevent drying. Allow the starch jelly to cool a little, and then spread thickly on clean gauze or linen and apply to the crusted parts with a bandage. The poultice is left on for one hour, and when removed the crusts come off with the dressing. This procedure may be repeated, if required.

It is imperative that bacterial infections be considered in the light of the latest chemotherapeutic advances. Both penicillin¹⁷ and the sulfonamides have their special indications and are of great value, but it cannot be too strongly emphasized that these drugs, and in particular the latter, should never be administered or applied routinely, or in mild cases which may be expected to respond to other measures. The use of these drugs may sensitize the patient.



FIG. 6.—Crusted impetigo contagiosa.

so that at some later date, when they might be urgently needed for a more serious condition, their use would lead to serious reactions. Moreover, the number of reactions caused by these drugs is constantly increasing, so that not infrequently the management of the drug reaction becomes a more difficult problem than the condition for which it was prescribed. Recently Pillsbury¹⁸ has attempted to clarify the indications for these drugs. Thus for simple impetigo (Fig. 6), ecthyma, acute infectious eczematoid dermatitis, and acute pustular folliculitis, the application of a penicillin ointment containing 500 units per gram, for a period not exceeding five days, is prescribed. If the lesions are extensive, this can be supplemented by intramuscular injection of one cubic centimeter of penicillin in beeswax and oil, containing 300,000 units. This should be continued for a period of five days, at which time, if there is no improvement, the penicillin may be discontinued. In many cases in which penicillin proves inadequate, an ammoniated mercury ointment, not exceeding 2 per cent, may yield most satisfactory results. Bivings¹⁹ also used penicillin injections in impetigo with good results. He used 12,000 units in aqueous solution every three hours until improvement was obtained.

In cases of secondarily infected dermatitis, impetiginized eczema, or infected dermatophytosis, the parenteral administration of penicillin seems preferable. Although sulfonamides have not been recommended, for patients in whom penicillin is contraindicated or ineffective they may be given a trial locally and orally for three to five days. Soothing local antiseptic compresses have been found useful and may be prepared from solutions of 0.1 per cent silver nitrate, potassium permanganate in a 1:15,000 dilution, or bichloride of mercury in a 1:20,000 dilution.

A new substance for local application as an ointment or solution, 5 nitro-2-furaldehyde semicarbazone (Furacin), has recently been placed on the market. This new remedy may prove effective for patients in whom penicillin, ammoniated mercury, and the sulfonamides have failed. A contact dermatitis may be expected in about 10 per cent of patients treated with local medicaments.



Fig. 7.—Plantar wart. Necrosis due to nitric acid applied by patient.

VERRUCAE

Warts are seen much more frequently in children than in adults. The most common types include the verruca vulgaris and the verruca plana. Since warts have a definite tendency to disappear spontaneously in a varying period of time and as a rule cause little discomfort, it is wise to try simple, nonscarring, and harmless methods before resorting to more drastic procedures. However, if the warts are multiple and located on the face or in regions exposed to pressure, they may be unsightly or painful and require treatment. It is generally agreed that warts may disappear following suggestive therapy.^{20, 21} Some authors have claimed good results following simple painting of the wart with a dye or some other inert solution.^{22, 23} Fair results have also been obtained by application of various local caustics and antiseptics, such as:

R Mercurý bichloride	2 per cent
Salicylic acid	10 per cent
Alcohol, 95 per cent	q.s.
or	
R Salicylic acid	10 per cent
Flexible collodion	q.s.

Each wart is treated daily for several weeks. Although electrodesiccation is probably the best treatment when only a few warts are present, this method is usually frightening to young children.

Verruca plantaris (Fig. 7) and *acuminata* are uncommon in children

DERMATITIS DUE TO PLANTS

Types of dermatitis venenata, or contact dermatitis, whether caused by ivy, oak, sumac, or lac trees, are clinically similar. The cutaneous reaction is due to a poisonous oil found in the sap. Actually only a single genus, *Rhus*, is responsible for the dermatitis. The toxic resin is not air-borne, the poisonous effect is the result of direct contact of the skin with the plant itself, or with animals who have been in direct contact with the plant. Plant dermatitis usually develops following previous sensitization to the oil. The best preventive measure up to the present has been avoidance of contact with the plant. The administration of extracts of the poison in the hope of desensitizing the patient, whether, by the oral or parenteral route, has proved disappointing. Eradication of the poisonous plant constitutes by far the best preventive.²⁴ Although preseasonal immunizations may prove effective in preventing or moderating the seasonal attack, the results of this method have been generally unsatisfactory. Such therapy is valueless during the attack, and may even lead to exacerbation of the symptoms. Following known exposure by contact with the plant, a thorough washing of the exposed area with ordinary laundry soap and plenty of water is recommended. This procedure should be followed by free use of alcohol rinses. The contents of the vesicles are not autocontagious as is popularly believed. All bullae should be opened aseptically and drained. A prescription which has been found useful contains the following:

Rx Menthol	0.07
Pulverized alum	8.0
Boric acid	15.0
Powder	± 1

This is placed in six glasses of tepid boiled water, to be used as compresses. Aluminum acetate solution, 1:20, may also be used for this purpose. If secondary infection is present, lesions on the trunk may be treated with compresses saturated with potassium permanganate solution 1:8,000.

Recently Witherspoon²⁵ obtained good results by applying the following emulsion every two hours: 1 per cent of phenol or menthol, 10 per cent sodium perborate, and emulsion base q.s

When itching is intense, ice-cold compresses may afford relief. This type of dermatitis is self-limited, and after about two weeks the lesions subside, providing there is no secondary or reinfection.

MILIARIA AND INTERTRIGO

These conditions occur most frequently in the summer and in those who perspire excessively. Perspiration²⁶ plays an important part and may lead to impetigo, furunculosis, and formation of small pustules. In some instances the condition is caused by yeasts or fungi. The children must be kept very

clean, using plenty of water but avoiding harsh soaps. Physical exertion should be kept at a minimum, and, if possible, the child should be kept in a cool atmosphere. In cases of obesity, dietary control and restriction of fats are in order. The following prescription is recommended as a dusting powder:

R Menthol	0.03
Magnesium oxide	
Zinc oxide	
Bismuth subcarbonate	āā 8.0
Talc	
Zinc stearate	āā 4.0

This is used freely, and if pustulation is present, one per cent mild mercurous chloride may be added. In intertrigo, a 2 to 5 per cent tannic acid spray yields good results.



Fig. 8—Cavernous angioma since birth.

AMMONIA OR DIAPER DERMATITIS

This disease is also known as gluteal erythema, Jaquet's dermatitis, or napkin dermatitis. It is one of the most common eruptions encountered in infants and young children. In addition to the irritation of the skin produced in the area coming into contact with the wet diaper, irritation of the meatus may develop. It is the consensus and has been demonstrated that the causative organism of this condition is *Bacillus ammoniogenes*, a saprophytic, gram-positive bacillus, which is found in the feces. This organism decomposes the urea in the urine and liberates free ammonia. The wet diaper plus warmth provides a favorable condition for culture of the organism with liberation of excess amounts of ammonia.

In cases of ammonia dermatitis, the first proviso entails prophylaxis, i.e., frequent changing of diapers and the use of diapers which have been freshly boiled and rinsed in a suitable antiseptic. Bichloride of mercury, which was formerly used for this purpose, has been abandoned as being dangerous and yielding uncertain results. Boric acid rinses are ineffective. Recently a quaternary ammonium compound, paradi-isobutyl-cresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate, known commercially as Diapene, has been recommended.²⁷ One tablet dissolved in two quarts of water yields a 1:25,000 solution. The diapers are soaked for ten minutes, then wrung and dried. Of fifty children, forty responded to this treatment in one week. As an exclusively preventive measure, only the night diapers need be rinsed in this solution. Children who suffer from this skin affection should be placed on a neutral diet, and overfeeding and diarrhea should be avoided. Various protective creams are available for application at night to prevent irritation of the skin by the liberated ammonia (Baby Protective Cream, Breck).

VITAMIN DEFICIENCIES

The relation of vitamin deficiencies to skin disease must be kept in mind, and whenever such deficiency can be demonstrated, an attempt should be made to supply the needed vitamin. Many cases of seborrhea, pellagra, and ariboflavinosis respond to vitamin therapy. Pityriasis rubra pilaris, keratosis pilaris, keratosis follicularis, and certain constitutional diseases associated with excessive keratinization are benefited by vitamin A therapy.²⁸ Calciferol, or vitamin D₂, in large doses has yielded curative results in lupus vulgaris.

VASCULAR NEVI

Many different types of nevi occur in infants and children. The most important and most frequently seen are the vascular group. Such vascular anomalies may not be present at birth, but develop early in infancy or childhood. The familial tendency is low, and these lesions occur twice as often in females as in males. They usually grow rapidly in children up to 6 months of age, and then remain stationary. Clinical diagnosis is easy.

Classification of Vascular Nevi.—

1. Nevus araneus, spider or stellar nevus: of capillary origin; flat lesion.
2. Nevus flammeus, port-wine stain, port-wine mark, capillary hemangioma: of capillary origin; flat lesion.
3. Hemangioma simplex, strawberry or raspberry mark: of capillary origin: raised lesion.
4. Cavernous angioma: of capillary origin; raised lesion.
5. Lymphangioma.
6. Combinations of the above types.

Treatment of Vascular Nevi.—

Spider Nevus: This type is infrequent, and is easily cured by lightly touching the central capillary with the desiccating current. The usual location is on the face.

Nevus Flammeus: This type, too, is found most frequently on the face. The lesions are composed of capillaries, are absolutely flat, and the color varies from pink to deep red or purple, or may be mixed. There is no known treatment for these blemishes, although sporadic cases have been reported as showing some improvement following application of grenz rays or tattooing.

Hemangioma Simplex: These nevi involve only the superficial vessels. They may be present at birth, or appear shortly thereafter. They begin as a pin-point red area, which gradually becomes raised. They are red in color and may be slightly lobulated. They tend to enlarge, but may disappear spontaneously or following trauma. However, if trauma occurs, scarring may result. Ideal results are obtained in this type of nevus with beta-ray radium therapy, and the change observed following such treatment is often spectacular. Sometimes a single treatment suffices. For the deeper lesions, gamma-ray applicators are used. This type of radiation should not be applied in the vicinity of the eyes or over the epiphyses, since in these regions the effects may be harmful.

Contact x-ray therapy has also yielded good results in hemangioma simplex, as has the injection of sclerosing solutions,²⁹ such as 10 per cent of quinine hydrochloride and 10 per cent urethane (ethyl carbamate) solutions.

Electrocoagulation and carbon-dioxide ice are not recommended for exposed skin areas because of the scarring involved.

Cavernous Angioma: This is the most common of all the vascular nevi (Fig. 8). Although these lesions also may disappear spontaneously, it is the consensus that treatment should be applied early in infancy. It is difficult to foretell whether a spontaneous disappearance will occur. For this reason early treatment is recommended to prevent scarring and deformity. Good results have been obtained with the following methods: sclerosing injections, surgery, radium, electrocoagulation, carbon-dioxide snow, and x-ray. The method chosen will depend upon the location, duration, and size of the lesion, and the age of the patient. In many instances, a combination of these treatments has yielded good results.

SUMMARY

Certain dermatoses which affect children exclusively or predominantly are reviewed, including infantile eczemas, papular urticaria, tinea capitis, and angiomas. Since the skin of the child is more sensitive than that of the adult, greater care is required in prescribing remedies in order to avoid injury. A brief summary is presented of the latest methods of treatment of the more common dermatoses.

On the whole, the dermatoses of children respond satisfactorily to treatment, a very essential prerequisite for successful therapy being an initially correct diagnosis. Progress in any branch of medicine affecting dermatology, as in allergy, skin tests, the study of bacterial, parasitic, and fungous diseases, of nutritional, metabolic, or hormone disturbances, in processes of immunization, as well as in the application of new drugs including the sulfonamides and antibiotics, will, of course have repercussions in pediatric dermatology. It is imperative that the significance and effect of new discoveries in relation to the

skin of infants and children be determined. This will permit a fuller utilization of the discoveries and reduction of undesirable reactions to a minimum. In attempting to evaluate the probable end result of any given therapy, it is necessary to take into consideration the changes that are to be expected due to growth and maturation of the tissues.

500 CENTRAL MEDICAL BUILDING.

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Clinical Conference

CONFERENCE AT THE ST. LOUIS CHILDREN'S HOSPITAL

FEB. 13, 1948

DR. ALEXIS F. HARTMANN, CHIEF OF STAFF

Case 1. Neuroblastoma

DR. WALTER KENNEDY.—C. J. M., a 21-month-old white female infant, was admitted on Oct. 27, 1947, and expired on Feb. 3, 1948. She was apparently in good health until June, 1947, when she developed fever and cervical adenopathy, followed by bilateral otitis media. Symptoms subsided following bilateral myringotomies and sulfadiazine. One month later the infant developed fever, sore throat, albuminuria, and pyuria. There were no other findings referable to the urinary tract, and the symptoms subsided after treatment with penicillin and sulfadiazine. Approximately one month before entry, the right knee was stiff and painful for three days. Three weeks prior to entry the patient again developed fever and complained of dysuria. She appeared quite pale, and immediately before her admission to the hospital her skin developed a yellowish tinge. Listlessness, anorexia, and weight loss had been present since July. Past and family histories were nonrevealing.

Physical examination on admission revealed a well-developed, moderately well-nourished, pale, listless infant who appeared chronically ill. The skin was slightly yellow and pale. The scalp veins were prominent. There was a small, moderately firm, nontender mass, which appeared to be attached to the left temporal bone. The mucous membranes were pale. The preauricular and postauricular nodes were enlarged. Two firm, nonmoveable masses were felt in the left upper quadrant of the abdomen. The spleen was not palpable. The liver edge was felt 1 cm. below the costal margin. Physical examination was otherwise not remarkable.

Laboratory examination revealed hemoglobin of 6.4 Gm. and a white blood count of 14,000, with 1 myelocyte, 1 juvenile cell, 6 stab cells, 33 segmented cells, 53 lymphocytes, and 7 monocytes. Blood Kline and tuberculin tests were negative. Urinalysis, serum calcium, phosphorus, N.P.N., total proteins, and bone marrow studies were all normal. An I.V. pyelogram revealed no abnormality. On x-ray examination, many small radiolucent areas were seen in the calvarium, mandible, ribs, and scapulae. In the calvarium, these areas appeared to be within the marrow cavity but extended to the inner and outer tables.

Exploratory laparotomy revealed a tumor mass which appeared to be an enlarged lymph node. This was removed for biopsy and diagnosed as lymphosarcoma by the Department of Surgical Pathology. However, Dr. Margaret Smith, of the Department of Pathology, felt that it was a neuroblastoma. Irradiation was administered to all palpable tumors and to areas of bone showing

abnormal radiolucency. Following treatment, the tumor appeared to recede. During treatment the red and white counts diminished and the infant developed bleeding tendencies, so that blood transfusions were required frequently. Despite continued x-ray therapy, the liver gradually enlarged, and the patient developed severe epistaxis, respiratory wheezing, and coarse breath sounds. X-ray of the chest at this time showed an area of rounded pulmonary infiltration just lateral to the right hilus. Collapse of the eighth and tenth thoracic and the second lumbar vertebrae occurred, due to extension of the tumor. The subsequent course was downhill, and the patient expired on Feb. 3, 1948. The clinical diagnosis was neuroblastoma, with multiple metastases.

DR. HENRY T. LANG.—The body is of a fairly well-developed, moderately emaciated, 25-month-old female child weighing 10 kg. There is marked pallor of the skin and mucous membranes with numerous petechiae and ecchymoses in the skin of the entire body. A soft, fluctuant subcutaneous mass, 4 by 5 cm. in diameter, with a central, transverse, partially healed incisional wound containing viscid blood and soft, gray, hemorrhagic tissue is present in the anterior axillary fold. There are extensive ecchymoses in the skin of the superior palpebrae, but there is no proptosis of the eyeballs. Otherwise, the eyes are not remarkable. The head is large, measuring 62 cm. in the occipital frontal circumference, as compared to a normal of 48 cm. There is a 2 to 4 mm. separation of the bony sutures, and a large, soft, 2 by 3 cm., nonbulging anterior fontanel. On removing the brain, there is extensive infiltration of tumor in the calvarium which measures 2 to 3 mm. in thickness, and in the dura, forming a mat of tissue, 4 to 12 mm. in thickness, into which project many small spicules of bone, over the parietal and occipital lobes of the brain. This mat consists of a hemorrhagic, soft, friable, mottled, gray and dark red tissue. A large, soft mass of hemorrhagic tumor tissue, 4 by 3 by $2\frac{1}{2}$ cm. in diameter, adherent to the dura, causes a compression defect in the left occipital lobe of the brain. Similar tumor involvement of the superior sagittal sinus is seen at one point. The brain itself is not remarkable, otherwise, except for slight subarachnoidal hemorrhage over the parieto-occipital regions, bilaterally.

In the peritoneal cavity, in the region of the left adrenal, there is a large, lobulated, irregularly round, encapsulated tumor mass, measuring 5 by 4 by $3\frac{1}{2}$ cm., adherent to the capsule of the left kidney but not involving the kidney. On the capsular surface of this mass, there is an irregular remnant of adrenal tissue, 6 by 18 mm., which reveals the usual differentiation into cortex and medulla. The cut surfaces of this mass consist of soft, fluctuant, dark red tissue separated into small, irregular lobules by narrow and broad fibrous septa. The lobules vary greatly in consistency, some containing viscid bloody material, some a soft, grayish red granular tissue, and others irregular yellow foci of necrotic material in which there is deposition of calcium. The right adrenal appears normal although there are nodules of tumor in the surrounding tissue.

The kidneys are not remarkable except for scattered petechiae in the pelvis of the right kidney.

There are numerous metastases of the tumor. For example, multiple large, soft, nodular masses are found matted together encircling the left renal pedicle, and similar masses are present in the aortic, iliac, hypogastric, peripancreatic, portahepatic, tracheobronchial, and anterior mediastinal lymph nodes. These nodes present the same characteristics as the primary tumor mass. The superior vena cava is displaced anteriorly, and is partially compressed by a large mass of tumor in the anterior mediastinum.



Fig. 1—Cortical surface of right kidney, cut surface of left kidney, and cut surface of main mass of tumor involving the left adrenal gland



Fig. 2.—Intra-abdominal metastases

The liver is enlarged, weighing, 1,420 Gm., and contains several irregular foci of tumor involving approximately two-thirds of the right lobe and one-third of the left lobe. The tumor as elsewhere consists of numerous small lobules of soft, dark red and gray tissue, separated by broad fibrous septa with multiple foci of necrosis.

The spleen is enlarged, weighing 60 Gm., shows prominent Malpighian bodies and fairly firm red pulp, but is otherwise not remarkable.

There are 25 c.c. of clear yellow fluid in each pleural cavity. The lungs are partially collapsed with linear and dark red subcrepitant depressed foci of atelectasis and slight marginal emphysematous blebs in all lobes; on section, prominent vascular markings are seen. There is watery and viscid brown-tinged mucus and gastric contents in the trachea and bronchi with brown discoloration of the mucosa.

The heart and pericardial cavity are not remarkable except for scattered petechiae in the endo-, myo, and epicardium.

DR. PARKER R. BEAMER.—Dr. Lang and Dr. Geren, the resident in Pathology, have supervised preparation of some excellent pictures and photomicrographs of the tumor observed in this child's body at autopsy.

Fig. 1 illustrates the cortical surface of the right kidney, the cut surface of the left kidney, and the cut surface of the main mass of tumor involving the left adrenal gland, regarded as the probable site of origin. The mass is ovoid, slightly lobulated, soft, and delicately encapsulated. Section through the tumor reveals dark red, hemorrhagic tissue, which is divided into closely packed, irregular lobules by fine and moderately coarse fibrous septa. In several areas there are irregular, soft, yellow foci interpreted as foci of necrosis.

Fig. 2 demonstrates the intra-abdominal metastases. Several soft ovoid masses, varying in size, are found matted together about the left renal pedicle and in lymph nodes along the aorta and in the perirenal and periadrenal regions. The internal structure of these masses is similar to that seen in Fig. 1.

A photomicrograph of the primary tumor, in the region of the left adrenal gland, is shown in Fig. 3. A delicate fibrous capsule surrounds a mass of tumor cells, within which there is a large, irregular, necrotic focus comprised of finely and coarsely granular acidophilic material and small clumps of nuclear debris. The histologic structure of the adrenal gland is not unusual in character.

Fig. 4 is a section from a lymph node which is the site of one of the many metastases. The characteristic histologic structure of neuroblastoma is demonstrated well. The entire field is composed of numerous cells, all of which prove to be of one cellular type. Most of the tumor cells are small, measuring about 7 to 9 μ in diameter, and their nuclei are hyperchromatic. In general, there is a rather striking resemblance to lymphocytes. In other instances, the cells are slightly larger than lymphocytes, and the nuclei may assume a vesicular type of internal structure. The cytoplasm is scant to moderate in amount, and the staining reaction is slightly acidophilic or amphophilic. Some cells reveal a tendency for the cytoplasm to extend outward into poorly defined fibrillike processes. This characteristic is not as evident in this particular case as it is in other examples of neuroblastoma which we have observed. Although the main body of the tumor, either in the primary site or in metastases, is composed of tumor cells arranged singly or in small clumps with no orderly pattern, there are several foci in which the tumor cells form pseudorosettes. The cells are arranged in a circular pattern about a central area composed of fine, delicate, fibrillary material in a loose, matlike arrangement. This characteristic varies considerably in different regions but is well demonstrated in Fig. 4.

For several years these tumors were regarded as lymphosarcomas, and it was not until 1910 or 1911 that Wright recognized them as a separate entity and called them "neuroblastoma." This name has been deprecated by some investigators, who believe that the term neuroblastoma is not descriptive of the true nature of the tumor cells. The tumor is known also as "neuroblastoma sympatheticum," "sympathoblastoma," and "sympathicoblastoma." All of these terms are used to designate a malignant tumor which arises in the sympathetic nervous system. The tumor may arise in the adrenal medulla and in sites such as ganglia near the adrenal gland, the organ of Zuckerkandl, the celiac plexus, and in other ganglia of the sympathetic nervous system. Most of the tumors occur in children under the age of 4 years, although occasional examples are encountered in older children and even in adults.

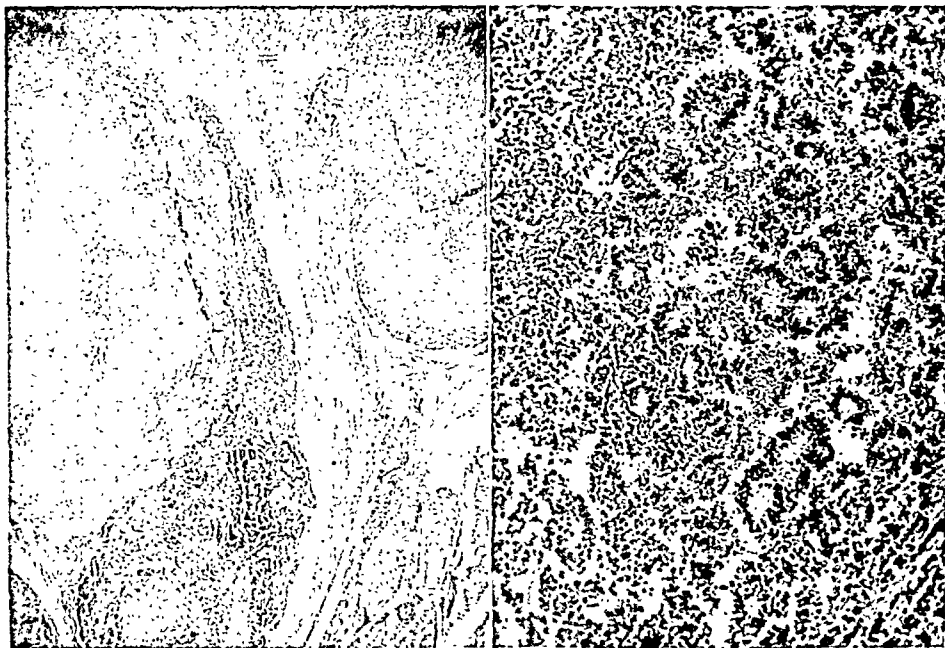


Fig. 3.

Fig. 3.—Photomicrograph of primary tumor, in the region of the left adrenal gland.

Fig. 4.

Fig. 4.—Section from a lymph node, the site of one of the many metastases.

The excellent schema of Bailey and Cushing may serve as a working outline in considering the derivation of cells which comprise tumors known as neuroblastoma. In the central nervous system, primitive medullary epithelium may delineate along five general lines:

1. Apolar neuroblasts, which subsequently develop into three types of polar neuroblasts and finally into neurones.
2. Medulloblasts, which give rise to oligodendroglial cells or may develop into unipolar types of spongioblasts and neuroblasts.

3. Primitive spongioblasts, which differentiate into fibrillary and protoplasmic types of astrocytes.

4. Cells comprising pineal parenchyma

5. Choroidal epithelial cells.

In the peripheral nervous system, where neuroblastomas arise, there may be a somewhat analogous derivation in that migrating indifferent cells of the ganglionic crest (the counterpart of medulloblasts of the central nervous system) may differentiate into five general categories.

1. Sympathoblasts, which in turn develop into (a) polar neuroblasts or (b) chromaffin cells and pheochromocytes.

(2) Bipolar neuroblasts, which subsequently develop into mature ganglion cells.

(3) Meningoblasts, which are the cells eventually forming the leptomeninges.

(4) Capsular cells.

(5) Neurilemma cells.

The cells comprising the neuroblastoma are, therefore, relatively primitive cells derived from migrating indifferent cells of the peripheral nervous system with capabilities of developing into mature ganglion cells. Within any one tumor an observer may find different stages of this development to a more mature type of cell.

Fig. 5 illustrates a section taken to demonstrate a metastatic focus of tumor in the liver. In a well-defined area with a poorly demarcated irregular edge, the usual architecture of the liver is replaced by numerous tumor cells, occurring as single cells or in small irregular clumps. Cytologically, these cells are identical with those seen in the primary tumor and in other metastases. Throughout the sinusoids of the liver there are scattered, individual or small groups of neuroblastoma cells. Vessels in the portal areas at the periphery of hepatic lobules contain large numbers of tumor cells, as shown in Fig. 6.

Fig. 7 reveals numerous tumor cells individually and in small groups, some in the form of pseudorosettes replacing a part of the usual erythroid and myeloid elements. There is a slight relative hyperplasia of myeloid cells.

A section from the calvarium (Fig. 8) demonstrates an advanced degree of infiltration by neoplastic cells with associated destruction of bony structures. Tumor does not invade the brain itself but impinges upon it, with resulting compression of the adjacent soft tissue.

For some years neuroblastomas have been considered as occurring in two clinical types. The Pepper variety is that in which there are conspicuous metastases in the liver and abdominal lymph nodes, whereas in the Hutchinson variety the metastases are noted first in the skull and periorbital tissues and subsequently in other bones of the body. In general, a tumor of the Pepper variety was considered to occur more often in the right adrenal gland, and that of the Hutchinson type was encountered more frequently in the left adrenal

gland. Approximately 10 per cent of neuroblastomas are reported to occur bilaterally. Frequently, a neuroblastoma of either adrenal gland does not behave according to the pattern just described, and there is little reason to perpetuate such designations.

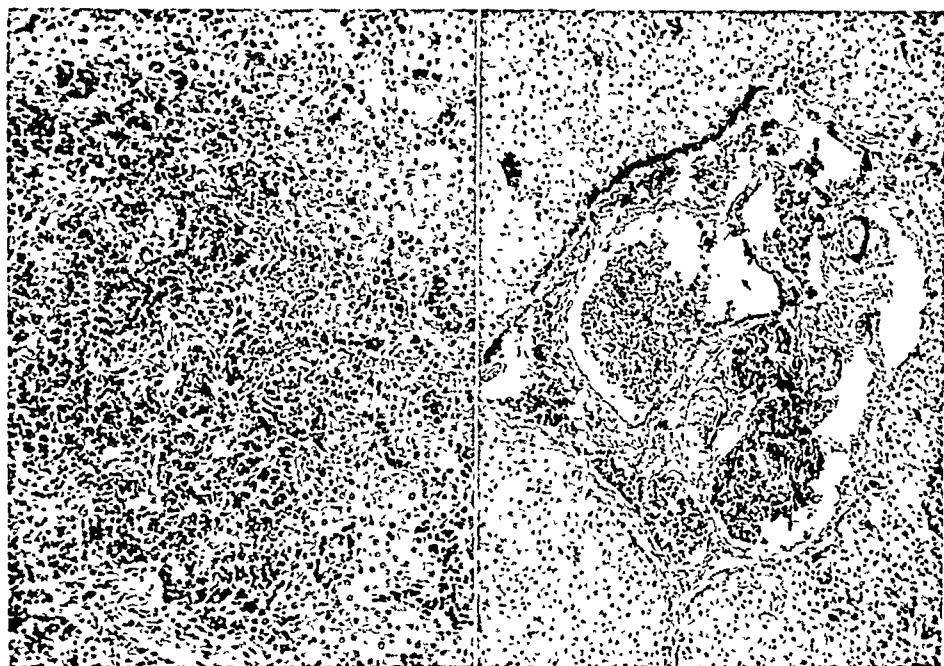


Fig. 5.

Fig. 6.

Fig. 5.—Section demonstrating metastatic focus of tumor in the liver.

Fig. 6.—Showing vessels in portal areas at periphery of hepatic lobules, which contain large numbers of tumor cells.

Dr. Sidney Farber* reported a study of 301 malignant tumors encountered in patients at the Children's Hospital in Boston. During the ten-year period immediately preceding the study, forty tumors from Dr. Farber's series were diagnosed as neuroblastoma by histologic study of biopsies and/or masses removed at operation. At a later date, Wyatt and Farber† published a more complete review of the roentgenologic and histopathologic studies of these patients. Roentgenologic studies were performed on thirty-four of the patients. Most of the tumors demonstrated in this way were found in the abdomen (seventeen instances), always in the dorsal regions. Next in frequency was the posterior mediastinum. The remainder arose in various other locations along the sympathetic chain from the cervical region to the pelvis. Most of the metastases to soft tissue occurred in the orbits (five instances) and the meninges (six instances). Metastases to bone were demonstrated roentgenologically in fifteen of the thirty-four patients, bilateral involvement of one or more

*Farber, S.: *Am. J. Dis. Child.* 60: 719, 1940 (abstract).

†Wyatt, G. M., and Farber, S.: *Am. J. Roentgenol.* 46: 185, 1941.

regions of the skeleton occurring in all but one of these. Sites most frequently involved by symmetrically occurring metastases were the shaft of the humerus, the distal portion of the femur, and the pelvis.



Fig. 7.

Fig. 8.

Fig. 7.—Showing numerous tumor cells, some replacing part of the usual erythroid and myeloid elements.

Fig. 8.—Section from calvarium, demonstrating advanced degree of infiltration by neoplastic cells with associated destruction of bony structures.

For purposes of evaluation, Dr. Farber classified treatment of these patients into five categories:

1. Complete excision of the primary tumor with no irradiation.
2. Removal of a biopsy specimen from an inoperable tumor, which had not metastasized, with no irradiation.
3. Partial removal of a primary tumor, which had not metastasized, followed by irradiation of the remaining tumor.
4. Removal of the primary tumor and biopsy of the metastasis to the liver, with subsequent irradiation.
5. Complete or incomplete removal of a tumor which was undergoing differentiation into a ganglioneuroma, with and without subsequent irradiation.

It should be noted that the series includes patients who received varied treatment, ranging from that which might be curative to that which was known to be ineffective as a curative measure. According to my interpretation of Dr. Farber's conclusions, the prognosis is exceedingly grave when metastases have occurred in bone. As I recall, the group in Boston had no success in treating

these patients. However, they were successful in treating (1) patients with neuroblastoma which had not metastasized, and (2) those in whom there were metastases to the liver and abdominal lymph nodes, where it was believed that most of the primary tumor could be removed and the remainder of the primary tumor and metastases could be radiated postoperatively.

Any abnormal solid mass found in a child should be considered a malignant tumor unless it is regarded as benign following adequate histopathologic studies. As soon as the diagnosis of neuroblastoma is made by study of surgically removed tumor, radiation therapy should be instituted in every case, according to Wyatt and Farber. Despite the fact that no cures were obtained when irradiation was employed after widespread metastases had occurred, Wyatt believes that the response was such as to encourage further efforts with this type of therapy. Dr. Geren communicated with Dr. Farber just a few days ago to secure the latest information regarding his experience with neuroblastoma. He reports by letter that they now have in their series six patients who have been alive for periods varying from two to ten years after treatment was instituted, even though metastases had occurred by the time the diagnosis was made. This experience suggests that the prognosis may in some instances be somewhat better than that usually offered in such cases.

DR. ALEXIS F. HARTMANN.—There are a few remarks that I would like to make about this child. I regret that we did not have some colored films of this baby. Words simply cannot as well describe the picture in a way that will fix it in your memories. We showed this child twice before here, once a few days after admission when a diagnosis had not as yet been made. We stated at that time that despite the fact that this baby was sent here with the diagnosis of chronic urinary tract infection and chronic respiratory infection, the thought being that the baby would be worked up from the standpoint of the kidney primarily and of the ears and mastoids secondarily, the first impression that everyone had of this baby was that he probably had a malignancy or leucemia. The color of the baby was very unusual. In addition to the marked anemia there was a peculiar lemon-yellow tint that we associate with the cachexia of malignancy. There were hemorrhages which were striking and not to be expected from ordinary chronic otitis media or pyuria. The enlarged glands made one suspicious of something more significant. The appearance of the scalp with its prominent veins and with tumor masses that could be seen and felt and that seemed to be attached to the underlying bone or periosteum was striking. Shortly before death, every vein in this child's scalp had enlarged tenfold and was distended, and the whole appearance had become that of a Medusa-head. Of course, at postmortem, with the blood gone from the veins, the distention of the vessels would not be so marked.

I should like to ask Dr. Beamer one question. During the exploratory laparotomy, one of the two abdominal masses was largely removed for purposes of study. After irradiation the other mass disappeared so that it was no longer felt, and the masses on the scalp, on the mandible—in fact, all superficial masses

of tumor tissue—disappeared rapidly; the original cervical lymph nodes all became small and shotty, and the impression was that there was decided response to x-ray and that perhaps treatment was at least partially successful. Now, is there anything at all about what you see at post-mortem that would indicate that there was that sort of x-ray response? What you showed us would make us think that perhaps there was not.

DR. BEAMER.—Recession of palpable masses is frequently observed when neuroblastomas are irradiated. This would not necessarily indicate, however, the complete destruction of tumor in that region. Tumor cells which are not destroyed by a given dose of irradiation may, of course, give rise to recurrent masses or new ones. In this particular instance, I see no significant evidence of the effect of irradiation unless one ascribes the necrosis in the abdominal tumor masses to that cause. However, the necrosis may be spontaneous. Related to this point is an observation that has been made by Dr. Farber and others namely, that neuroblastomas may undergo spontaneous hemorrhage and necrosis and disappear without any treatment whatsoever. Neuroblastoma may also undergo spontaneous maturation and differentiate into a ganglioneuroma, which is benign. Such a case was reported by Cushing and Wolbach.*

Case 2. Tuberous Sclerosis

DR. ROBERT FRIEDMAN.—The next case is that of a 20-month-old female infant, who was admitted to Children's Hospital with the chief complaint of attacks of jerking of the extremities and unconsciousness. The onset of the illness was at the age of 7 months. The mother noted at that time that the child would nod her head, jerk the extremities, and the eyeballs would roll up. The second attack occurred a month later when the patient had a cold. At this time the child could not be awakened, vomited, and became quite limp. She was found to have an acute bronchial infection, which subsided after proper therapy. Fasting blood sugar at this time was not low, according to the local physician. Two weeks before admission she again had an attack in which she became rigid and vomited. Each day before admission the child had about three such attacks lasting two to five minutes. These seizures consisted of jerking of the extremities, nodding of the head, and upward deviation of the eyes. Rarely such an attack would occur during the night, awakening the child. Afterward the child would usually go into a deep sleep. We witnessed one such episode when the child was in the admitting room. Since she has been in the hospital she has had no such seizures. The past history is of interest in that the patient has developed slowly, had difficulty walking, and does not talk. She has two siblings who had similar seizures. A brother, age 8, now has a mental age of 6. His attacks began at the age of 7 months. At that time he was placed on a two-hour feeding schedule with large amounts of glucose with apparent benefit. He was often unconscious for three or four hours during the attacks, and the mother stated he looked "yellow." One sister, who is now 10, also had attacks which

*Cushing, H., and Wolbach, S. B.: *Am. J. Path.* 3: 203, 1927.

appeared to be helped by high glucose intake. She is now doing quite well in school although she seems to have some behavior difficulty. Both the siblings had eruptions that appeared in the butterfly area of the face at the age of 2 years. They also had other areas of depigmentation and hyperpigmentation over the body. The sister had typical eye ground findings which Dr. Goodfriend will describe.

On admission to the hospital physical examination revealed a child who was somewhat retarded. Motions of the extremities were awkward, and the skin showed multiple areas of depigmentation. In the left fundus there was an area that was devoid of pigment. The laboratory studies revealed normal urine and hemogram, and the serum calcium, phosphorus, and glucose were within normal limits. The results of an insulin tolerance test were not remarkable. The EEG revealed waves that were highly consistent with convulsive disorder.

DR. JAMES GOODFRIEND.—Among the less common conditions associated with convulsive disorder, tuberous sclerosis is always mentioned, yet the disease is not very frequently diagnosed. In the past two years, however, six cases of tuberous sclerosis have been seen in this hospital, all bearing most of the major manifestations of the disease. This is the first instance in which we have been able to demonstrate the tendency for the syndrome to occur in several members of the same family. This is also the first instance in which we have been able to diagnose the disease before the appearance of the characteristic skin eruption (adenoma sebaceum).

The condition of tuberous sclerosis is a rather bizarre one in which there are multiple defects involving ectodermal structures. The brain contains nodules of varying sizes which are potato-like and, therefore, described as tuberous. Early, these may not be calcified, but later, calcium tends to be deposited in the nodules, making them visible on a plain film of the skull. In addition, various skin defects occur. The commonest of these is adenoma sebaceum, which is a brownish red, papular eruption which appears at birth or during early life and which remains essentially unchanged throughout the life-span of the patient. The individual papules vary from pin-point size to several millimeters in diameter; they are raised, firm, and glistening. They may be removed surgically, as has been done in two patients of our series. There are, in addition, various other skin manifestations which have been present in all of our cases. There are the changes in pigmentation which are present in this patient and in her two siblings. In addition, there is a characteristic thickened type of skin which appears in patches on these patients. This has been described as the Shagreen patch, and it closely resembles pigskin or elephant skin. The subcutaneous tissue cannot be identified clearly beneath the Shagreen patch. The characteristic triad of symptoms is completed by the presence of epileptiform seizures. These may be severe, generalized convulsive episodes, or they may be mild convulsive attacks as seen in this child. In one of our patients only severe disturbance of behavior associated with cerebral dysrhythmia has been noted. Most patients having attacks have been stated to deteriorate mentally, but that may well be a function of the convulsions rather than of the disease itself. Two of

our patients have been well controlled in regard to their convulsions and evidence no mental deterioration. One is in high school and doing acceptable work, and the other is in grade school. Although the latter shows some behavior disturbance, she has no difficulty in keeping up with her school work.

Both of the siblings of the infant now under discussion show characteristic adenoma sebaceum, defects of pigmentation, and Shagreen patches. The oldest child shows severe behavior disturbances, and the second child is moderately retarded mentally, as, we believe, is the youngest of the three siblings. The eye grounds of these patients show characteristic changes. The changes in the youngest patient have been described by Dr. Friedman, and the characteristic change which is most frequently seen in tuberous sclerosis can be noted in the examination of the oldest child. In the left retinal field there is an area about the size of the disc, which is composed of crystal-clear, translucent, grapelike bodies in clusters, which protrude from the retina and appear very much as if a pile of marbles had been placed there. A blood vessel is seen entering the lesion. The brother shows a very tiny but similar retinal defect.

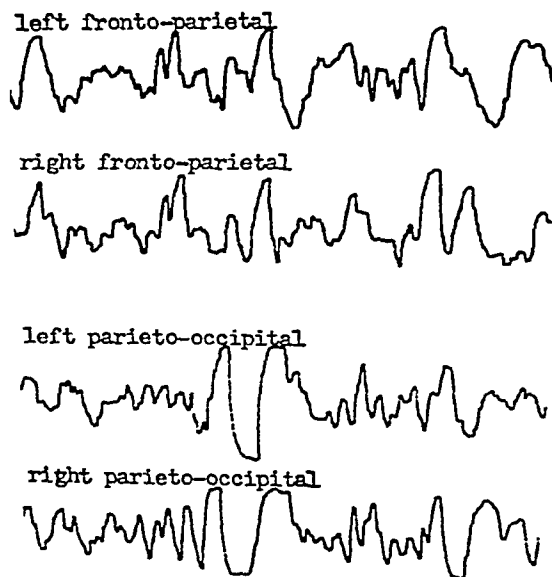


Fig 9—Electroencephalogram showing high spike waves followed by slow high voltage waves.

The outlook for patients with tuberous sclerosis has been altered by the introduction of effective analeptic drugs. In all of our patients at the present time we have been able to achieve almost complete freedom from seizures, and I think that that may make a considerable difference in their ultimate mental state. Certainly they have appeared to be much brighter and better adjusted, once their convulsive episodes have been cared for. The electroencephalograms on these patients show nothing characteristic but are usually composed of

Fig 10.



Fig. 11

Fig 10 —Patient's skull film showing one area of calcification which is easily identified and smaller areas which may be calcification or artifacts

Fig 11 —Skull film of oldest sibling showing cluster of calcifications

Fig. 12.



Fig. 13.

Fig. 12.—Skull film of brother showing more extensive calcification.

Fig. 13.—Pneumoencephalographic demonstration of noncalcified nipplelike projection into the ventricle.

markedly dysrhythmic waves and often show the type of abnormality which is exhibited by the present patient (Fig. 9) of high spike waves followed by slow high voltage waves. These may occur either focally or generally throughout the record.

If the nodules in the brain are calcified, they may be visualized on plain films. The patient's skull films show one area of calcification which can easily be identified and smaller areas which may be calcification or artifacts (Fig. 10). The films of the oldest sibling show a cluster of calcifications in essentially the same location; they may be seen both in the lateral and posteroanterior views (Fig. 11). The films of the brother show more calcification than do the films of the other two (Fig. 12). If the tumors are not calcified, they may be visualized by pneumoencephalography since the tumors frequently project into the ventricular system. In two previous patients nipplelike projections into the ventricles were well visualized (Fig. 13).

DR. HARTMANN.—I have a few comments I would like to make about these children, too. Sometimes it is interesting and instructive as to the way in which diagnoses are made. When I first heard about this family, the mother got in touch with us and stated that she wanted us to see this little baby who had hypoglycemia, and that two other children in her family also had hypoglycemia which began at about the age of this infant. Knowing my interest in hypoglycemia, you can imagine how excited I was when I thought I had run across a family of three, and then my disappointment when another cause for the convulsive disorder was found. It was even more amusing as to how the diagnosis was made. Just as we began to study this child we got a note from Dr. Seabee in Ophthalmology, stating that he had just seen the other children in the family, had looked at their eye grounds, and thought the diagnosis was tuberous sclerosis. So there was no delay in making the diagnosis in this child. It is important, however, to emphasize this point. It is not right to make a diagnosis of hypoglycemia unless you are sure about it because you might be overlooking something that has an entirely different prognosis and would require quite different therapy. We cannot go into all the details of hypoglycemia—the varieties and tests for making the diagnosis; however, you are familiar with what we have stressed here, and the history alone would suggest strongly that these children, if they had hypoglycemia, belong to a type that we have not previously encountered.

Case 3. Empyema

DR. LOUIS BUSH.—This 8-month-old white male child was admitted to Children's Hospital a little more than a month ago with chief complaints of fever, cough, and grunting respiration of one day's duration. The child had been ill at home with an upper respiratory infection for two weeks. This illness appeared to be of little consequence until the end of the first week, when the child had symptoms very much like those on admission. He was taken to the family physician, who ordered oral penicillin. The child improved, and after three days the medication was stopped. On the following day the symptoms returned, and the child was again taken to the physician, who prescribed a sulfonamide

and advised hospitalization. On the following day the child was admitted here. On admission the temperature was 40.5° C., the pulse 120, and the respirations 90. The child was pale and severely toxemic and cyanotic; the respirations were grunting, and there was flaring of the ala nasi. There were dry crusts in the nose and slight injection of both tympanic membranes. The heart was displaced to the right, so that the point of maximum impulse was at the left border of the sternum. The entire left side of the chest was flat to percussion, with breath sounds greatly diminished except for a small area of bronchial breathing in the left axilla. The right side of the chest was normal to percussion and auscultation except for a few râles over the right lower lobe. The liver was palpable three fingerbreadths below the right costal margin. The remainder of the physical examination was normal. The hemoglobin was 11.5 Gm. and the white blood cells 900, with 20 stab cells, 15 segmented cells, 63 lymphocytes, and 2 monocytes. The urine was normal. The serum carbon dioxide was 48.4 volumes per cent.

On fluoroscopy the left side of the chest was seen to be uniformly dark; a thoracentesis yielded 50 c.c. of thin yellow fluid, from which a pneumococcus Type 2 was subsequently isolated. Penicillin and streptomycin were instilled into the thoracic cavity through the thoracentesis needle, and the patient started on parenteral sulfonamides (sulfamerazine, sulfadiazine, and sulfapyrazine in combination). Supportive therapy in the form of parenteral injections of glucose, lactate Ringer's solution, and whole blood was also employed.

On the second day of hospitalization the child continued to do poorly, and more fluid was obtained by thoracentesis. A closed intercostal drainage was, therefore, instituted by the chest surgeons. The child's temperature became normal at this time, but his general condition did not improve and signs of involvement of the right lung and later of right pleural effusion developed after several days. Right thoracentesis produced yellow fluid, which proved sterile on culture, and closed drainage was also begun on that side. At this time, his ninth hospital day, the child showed signs of heart failure. A bloodless phlebotomy was performed with some resultant improvement in the patient's condition. An ECG showed myocardial degeneration suggesting coronary insufficiency. The child was digitalized. Slow improvement ensued, and after twelve days digitalis was discontinued. Drainage from both tubes has persisted until three days ago when the tube was removed from the right side of the chest; there is still drainage from the left. The temperature remains normal although no antibiotic or chemotherapeutic agents are now being employed. Respirations are still noisy, but not labored. The N.P.N and carbon dioxide are normal. Thoracic scoliosis has been gradually developing and is now very marked with the convexity to the right. The child is taking food and fluids fairly well and should leave the hospital as soon as drainage from the left side of the chest ceases.

DR. GILBERT B. FORBES—You might be interested in seeing the series of x-rays which were obtained in this baby, starting with Fig. 14, which shows infiltration and the appearance of fluid on both sides of the chest. There had been fluid in the left chest since the time of admission of the child to the hos-

Fig. 14.

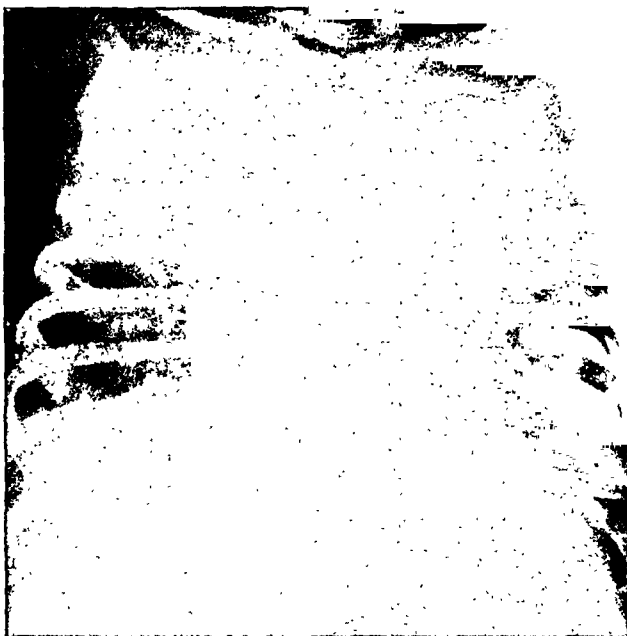


Fig. 15.

Fig. 14.—X-ray showing infiltration and appearance of fluid on both sides of the chest.

Fig. 15.—X-ray made during fourth hospital week showing appearance of some degree of scoliosis to the right.

pital. On the third hospital day a complication occurred in that an area of hyperresonance and decreased breath sounds appeared on the left side of the chest. Fluoroscopy was carried out and pneumothorax confirmed. This later subsided with re-establishment of effective intercostal drainage. The succeeding films show a very gradual change in the chest, and there is noted for the first time on the film which was taken during the fourth hospital week (Fig. 15) the appearance of some degree of scoliosis to the right. The film which was taken a few days ago (Fig. 16) shows that this scoliosis is much more evident and furthermore shows that the process in the left thoracic cavity has not been completely eliminated. There is uniform density over this area of the chest; there



Fig. 16.—Most recent film, showing scoliosis to be much more evident and that the process in left thoracic cavity has not been completely eliminated.

is still some displacement of the heart to the right. Physical examination of the chest elicits a dull percussion note, and the breath sounds are markedly suppressed in this area. The patient, therefore, presented several problems, the first one of which concerned control of the infection which was present during the early days of his hospital stay. Disappearance of organisms, subsidence of fever, and disappearance of an infectious blood picture were observed and can be ascribed to the medical therapy which was given—namely, penicillin, streptomycin, and sulfonamide drugs. The use of all three of these agents was necessary. Dr. Bush neglected to mention that the identification of the infecting organism as pneumococcus Type 2 was not made for some ten days after the child was admitted, and it was felt that in the absence of conclusive cultural data, the

broadest possible antibacterial coverage was necessary. The appearance during the second hospital week of an effusion in the right pleural cavity, where none before had existed, was confusing to us, and we are not yet able to explain it, nor are we able to explain definitely the picture of cardiac decompensation that the baby presented during the same period. There was marked edema; there was dyspnea; there were moist râles throughout the chest; and the baby seemed to respond clinically to a bloodless phlebotomy and later to respond slowly to the administration of digitalis. Whether the failure was due to toxemia accompanying the disease process or to a myocarditis on the basis of sulfonamide intoxication is not clear. The child unfortunately sustained an extraordinarily high level of sulfonamide drug of the order of 70 mg. per cent, which was accompanied by definite signs of renal irritation in the form of azotemia, albuminuria, and red cells in the urine. The azotemia has subsequently disappeared, and the urine is now normal. Whether or not the cardiac symptoms were a manifestation of sulfonamide intoxication we are unable to say. The child has weathered the infection, the pleural effusion, and the probable cardiac failure, and we are now left with one more problem still to be solved. This, I am sure, is more in the field of the chest surgeon than the pediatrician—namely, to clarify the process which is now going on in the left thoracic cavity and which is producing mediastinal displacement and scoliosis of the dorsal lumbar spine.

In an analysis several years ago of cases of empyema* seen at this hospital—and I might clarify the term *empyema* by stating that we excluded cases which were secondary to operative procedures or any degree of bronchiectasis or perforation of the mediastinum, or foreign body, etc., because they form a separate group—it was noted that the staphylococcus was very frequently the causative agent in young infants, accounting for most of the cases of empyema which were seen in infants under one year of age. In the past four years, since our previous analysis, we have seen twelve cases of empyema. All of these patients have received penicillin (Table I). In older children, there were no instances of primary staphylococcal empyema, whereas in young babies five out of the seven cases which we observed were due to the staphylococcus. Furthermore, it is noted that the incidence of empyema in this hospital is decreasing yearly. We feel that since the patients with primary pneumonia whom we now see and treat with penicillin and sulfonamides exhibit a lessened incidence of complications, the use of these therapeutic agents is responsible for the decrease in cases of empyema. It is noted that in the five-year period between 1934 and 1938 we saw in this hospital an average of twenty-four cases of empyema per year, an incidence of 7.1 cases per 1,000 admissions. In the next five-year period, 1939 to 1943 inclusive, the incidence was 3.7 per 1,000 admissions. For the past four years this figure stands at 0.97, so that the incidence as far as our own experience is concerned has decreased tremendously. We note that of these twelve patients, one died. This was a newborn infant in whom the diagnosis of empyema was first made at autopsy and in whom the presence of an infectious process

*Forbes, G. B.: J. PEDIAT. 29: 45, 1946.

in the chest was not suspected during life. One of the patients exhibited the complication of an accompanying pneumothorax. We have noted in previous compilations of cases of empyema, particularly those due to staphylococci, that roughly 40 per cent sustained a pneumothorax of small or large extent, and that this complicating feature must be taken into account in the management of empyema in small infants. I should like to emphasize two points in concluding: first, that we must consider in the differential diagnosis of this condition the fact that the staphylococcus plays a very important role in the causation of empyema in infancy, and next, that although we now have available powerful antibiotic agents, we still occasionally see complications such as have been manifested by this patient.

TABLE I. CASES OF ACUTE EMPYEMA

YEAR	PNEUMOCOCCUS	STREPTOCOCCUS	STAPHYLOCOCCUS	MIXED STREP. AND STAPH.
1944	4	0	1	
1945	0	1	1	
1946	1	0	2	1
1947	0	0	1	
Totals	5	1	5	1

DR. LEONARD KEMLER.—It is the feeling of the Chest Surgery Department that despite the help given by the antibiotics, once the diagnosis of empyema is made in an infant and the organisms demonstrated either by smear or culture of the pleural fluid, intercostal drainage should be established immediately. In adults we frequently wait for frank pus to form. However, in children it is felt that tension pneumothorax which may follow rupture of a peripheral abscess is averted if early intercostal drainage is instituted. We usually employ the intercostal drain as closed drainage for ten days to two weeks, following which it is customary to remove the drainage bottles, cut off the tube level with the skin, and gradually in the period of the next two or three weeks shorten the intercostal tube, eventually removing it. In this child, the pleural effusion on the right side cleared up much more quickly than that on the left, and consequently the tube on the right came out earlier than the tube on the left. It is our feeling that in this child the left side has developed marked pleural thickening, and we have been somewhat baffled by the scoliosis which has appeared. The explanation is offered that the child has an exuberant growth of granulation tissue and marked pleural thickening, which is pushing the entire mediastinum to the right side and causing scoliosis. If that is the case, eventually we might perform a decortication, but we are awaiting further developments.

DR. HARTMANN.—One feature about Fig. 16 that is probably most frequently overlooked is that the ribs are very close together on one side (left) as compared to the other. This is strongly suggestive of some atelectasis of the left lung. That lung has not expanded well, and physical signs are those of poor entry and egress of air. Taken with the other evidence of greatly thickened pleura, the film suggests that this whole lung is covered by thickened pleura and can't expand very well, and that is what is the matter. I think this was a very

common complication in older days, and actually there was a period in chest surgery when attempts to dissolve off this thickened fibrin were made by irrigation with Dakin's solution and other similar agents. This was not very successful.

Case 4. Hemophilia

DR. FRIEDMAN.—The next patient is an 8-year-old hemophiliac, who has had four previous admissions to Children's Hospital. These admissions were for bleeding of the cheek, laceration of the left leg, retroperitoneal hemorrhage, and hematoma of the abdomen. The present admission was for hemarthrosis of the right knee. The bleeding tendency was noticed shortly after birth when the patient was circumcised and bled very severely. The present episode of swelling and tenderness of the right knee began in May, 1947, when the patient received a sharp blow on that knee when he was playing. Following this, the knee became quite tender and swollen, but there was no discoloration. The swelling subsided for a while, only to return several times in the following month. The knee became increasingly involved so that movement at the joint became impossible. He was admitted to this hospital in December, 1947, and a cast was applied to the leg. He was followed in the clinic with the cast on for about seven weeks, and then it was removed. When it was removed, the joint was quite painful on motion and was flexed to an angle of about 130 degrees. Since there was no improvement the patient was again hospitalized, and an attempt was made to regulate his clotting time with the use of Cohn's Fraction I. Family background was of interest in that there was no history of a bleeding tendency for four generations.

The admission physical examination revealed an ecchymotic area about 5 by 5 cm. on the right thigh. The knee was swollen, tender, and painful, and flexed to about 100 degrees. X-rays which were taken of this joint will be shown by Dr. Klingberg.

The patient has a clotting time of fifty-eight minutes. Two-tenths gram of Fraction I was injected intravenously with decrease of clotting time to thirty minutes. This was followed by injections of Fraction I at six-hour intervals. On one occasion on the fourth day the clotting time was nearly normal. On the sixth day all treatment was discontinued, and on the seventh day we again started treatment with antihemophilic globulin, this time using a daily dosage of 0.4 Gm. The clotting time was reduced to two minutes forty-five seconds, which is within normal limits. On continuation of therapy, however, the clotting time increased, and because of the thrombosis of many of the child's veins we have discontinued all injections.

DR. W. G. KLINGBERG.—This boy presents a typical picture of hemophilia as we see it in childhood. He is presented today to demonstrate the use of Fraction I. We have used it only for the past six months and in only three cases. Of the two earlier cases in which we have used Fraction I (the antihemophilic globulin isolated during wartime by fractionation of blood plasma) the first patient had a hemarthrosis similar to that of the present patient, but we did not employ the globulin intensively. What we thought were rather remarkable

figures, however, were obtained at that time with one injection of Fraction I (0.2 Gm.), with the reduction of the clotting time from two hours to fifteen minutes. The second instance in which we used Fraction I was in a hemophiliac who has been in this hospital some sixty times with many complications. During an admission when he had hematuria and evidence of retroperitoneal bleeding, an appreciable effect was seen with the use of Fraction I. The clotting time decreased from one hour to between ten and fifteen minutes. In this patient, too, the preparation was used only a few times. We admitted the present patient for intensive therapy with the idea in mind that if we could reduce his clotting time to normal and maintain it for an adequately long period we might be able to open the right knee joint, evacuate the blood, close the joint, and secure relatively good function. We administered the plasma fraction and obtained the results seen in Fig. 17. Unfortunately, the results were not too good, and less dramatic than Dr. Diamond reported to us recently. Dr. Diamond remarked at that time, however, that the results seen in Boston with Fraction I have been erratic. He mentioned four cases in which a knee joint that had been involved as in this instance was opened and evacuated with excellent results.

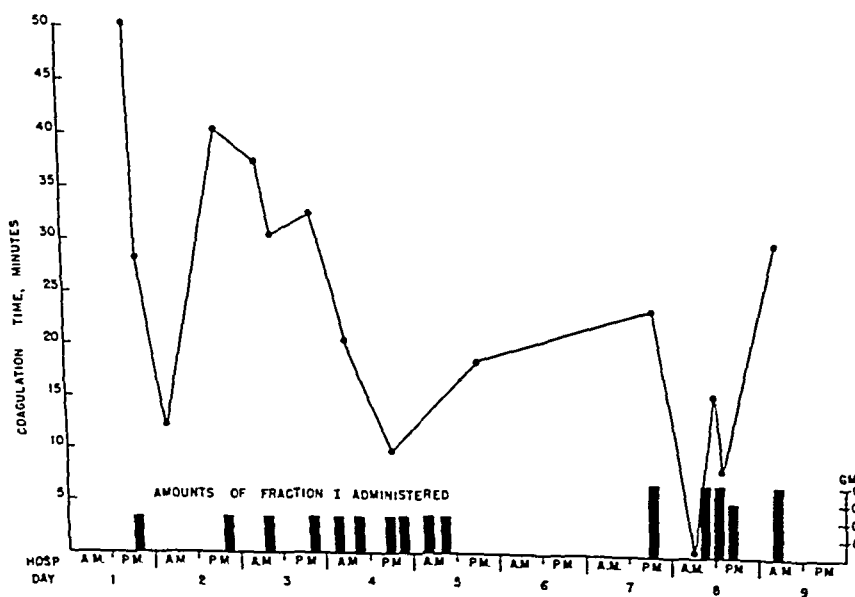


FIG. 17.—Response of coagulation time to administration of Fraction I.

The globulin has been given intravenously routinely. Its intramuscular use has produced variable results. We have given it intramuscularly on one occasion with very poor results on the clotting time and with much local pain. There is perhaps some little cumulative effect of the material when it is given at six-hour intervals. Even with the doubling of the dose to 400 mg. our best clotting time was two minutes forty-five seconds and despite repeated injections of the fraction, the clotting time increased to thirty minutes. Apparently there is some sclerosing factor in Fraction I as indicated by the tendency of

the veins which have been employed to become thrombosed. We are, therefore, unable to give repeated injections over a long time. We may be able to use each vein only two or three times. Consequently, over a period of ten days with repeated injections in this particular patient we have used up practically all of his available veins and of necessity have had to discontinue the injections.

Because of our variable results it may be interesting to mention a recent article by Craddock and Lawrence* of the University of Rochester, in which are reported two cases of hemophilia in adults who have become resistant to all present modes of therapy. With repeated transfusions of whole blood, plasma, or Fraction I, these two patients developed an apparent anticoagulant substance. Because of this development, regardless of the kind or amount of therapeutic agent employed, it was impossible to regulate the clotting time. A similar patient was reported some years ago. This anticoagulant reaction was investigated from every viewpoint. It did not inhibit any of the elements known to be involved in the clotting mechanism, such as prothrombin, thrombin, thromboplastin, fibrin, and fibrinogen. It was apparently not related to heparin in any way. The anticoagulant was found to be most concentrated in the gamma globulin fraction. Because of this it was thought to be an antibody, and it was postulated that the development of resistance to treatment might represent an antigen-antibody type of reaction. A specific precipitin against the antihemophilic globulin (Fraction I of Cohn) was demonstrated in the sera of both patients. It was, therefore, assumed that these patients had been immunized against the antihemophilic globulin by the repeated injections of whole blood, plasma, or Fraction I, that antibodies had been produced, and that these in turn prevented any subsequent regulation of the patient. This antibody added to normal blood would inhibit its clotting. I do not believe that this patient has developed any definite signs of having developed an anticoagulant as yet, but certainly one must think of this in view of our disappointing results.

The x-ray films of the right and left knee joints (Fig. 18) show a relatively normal left knee joint, but in the region of the right knee there is marked swelling of the soft tissues about the joint and no evidence of calcification within the joint.

DR. J. V. COOKE.—In commenting on the effect of various agents on coagulation times in hemophilia, I think it is interesting to review certain things. Originally, transfusion of whole blood was the method used for correcting the clotting time. It was believed that in this way platelets which decreased the clotting time were supplied to the patient. The recent use of Fraction I has raised some interesting points. I would like to review briefly some work that has recently been published by Brinkhaus in this connection. In hemophilic blood there is a delayed conversion of prothrombin into thrombin apparently because of slow liberation of thromboplastin from the formed elements of the blood, chiefly the platelets. Brinkhaus† has shown that after removal of the formed elements in normal blood by centrifugation, a delay in prothrombin conversion is noted with progressive lengthening of the coagulation time until,

*Craddock, C. G., Jr., and Lawrence, J. S.: *Blood* 2: 505, 1947.

†Brinkhaus, K. M.: *Proc. Soc. Exper. Biol. & Med.* 66: 117, 1947.

after long centrifugation, plasma is obtained which is incoagulable and which is called quasihemophilic blood. For example, after centrifugation for one-half hour, coagulation takes place in the normal range; after one to one and one-half hours it takes place in eighteen to twenty minutes; after two hours, in thirty-one minutes; and after twenty-two hours clotting requires more than thirty hours. The prothrombin content of such centrifuged plasma is normal. Addition of platelet suspensions to them reduces the clotting time to six to nine minutes. All such platelet-low or platelet-free plasma samples produced normal clotting time with whole hemophilic blood, but when tested with hemophilic platelet-free plasma, they gave coagulation times of about the same duration as the original plasma and no clot with quasihemophilic plasma. When platelet-free.



Fig. 15.—Films of right and left knee joints, showing relatively normal left knee joint, but marked swelling of soft tissues about right joint and no evidence of calcification within the joint.

recalcified hemophilic plasma was treated with (1) normal platelet suspension, or (2) hemophilic platelet suspension, or (3) platelet-poor plasma (centrifuged two hours), the clotting time constantly was twenty-eight to thirty-two minutes, but when platelet-free, recalcified hemophilic plasma was treated with (1) normal platelet-poor plasma plus normal platelet suspension, or (2) normal platelet-poor plasma plus hemophilic platelet suspension, coagulation occurred in six to eight minutes. Because of these findings Brinkhaus has hypothesized that normal plasma contains a factor necessary for the liberation of thrombo-

plastin from the formed elements of the blood, probably a platelet lysin. This thromboeytolysin is deficient in hemophilic plasma, and when supplied to the hemophiliac in normal blood or plasma transfusion, the platelets rupture in the normal manner, sufficient thromboplastin becomes available, and normal clotting occurs. Therefore, it is not the addition of normal platelets or platelets from normal blood that decreases the coagulation time in hemophilia, since the platelets in hemophilic plasma rupture normally after they are brought in contact with the thromboeytolysin of normal serum. That is apparently why plasma transfusions in hemophilia have the same good effect as whole blood transfusions in reducing the coagulation time, and it is probably why this particular fraction of normal plasma has a similar effect.

It is conceivable that if Fraction I is diluted with normal plasma or normal serum or with some other diluent, it might be much less corrosive in effect on the veins. This may be an important practical point in the treatment of hemophilias.

Case 5. Coarctation of the Aorta

DR. HERBERT MAZUR.—This is a 4-year-old white boy who entered the hospital approximately two weeks ago. About two and one-half years ago, according to his parents, a pulsation was noted in the lower portion of the right side of the neck. This pulsation persisted, but it did not seem to affect the patient adversely. The child has developed quite normally and has always been healthy. Never at any time has he complained of dyspnea or orthopnea; he has never had any cough, any tingling of the extremities, or any hemoptysis. He was seen in December, 1947, by the family physician, who told the parents that the patient had no palpable left radial pulse and referred him to Dr. Jaudon. On admission the patient was seen to be a well-developed, well-nourished white boy who was in no distress. His color was good, and his position on the Wetzell Grid indicated that his growth had been normal. There was an area of tiny dilated capillaries upon the skin of the left shoulder and the lower aspect of the neck on the right, representing the residuum of a small hemangioma for which he had received x-ray therapy some years ago. The eye grounds were normal. At the suprasternal notch and just to the right of it a marked pulsation and a slight bulging were noted. This pulsation could be felt superiorly along the right carotid and also laterally along the base of the neck on the right for four or five inches. Over this entire area a thrill could be felt, which was systolic in time and was transmitted to the interscapular region on the right. The blood pressure in the right arm was 140/90. In the left arm the systolic pressure could be heard coming in at 110, but it was very indistinct. No blood pressures could be obtained in the lower extremities. The pulse in the right radial artery was quite full and bounding; there were no pulsations felt over the left radial artery or in the area of the abdominal aorta or over the popliteal or dorsalis pedis arteries. Very faint pulsations were felt in the area of the left common carotid and over the femorals. The liver was enlarged to 4 cm. below the costal margin in the midclavicular line. There were no other significant physical findings. Since he has been in the hospital the patient has looked and felt

well; his blood pressure has varied from 110 to 140/ 80 to 90. The capillaries of the nail beds have been visualized; it was seen that the capillaries on the right were definitely more full, dilated, and tortuous than those on the left. In that connection Dr. Goldman has recorded the capillary pulsations. Following a fluoroscopic examination by Dr. Carson, two angiograms were made. In the second the aorta was visualized up to a point of probable coarctation. The surgeons advised an operation that is to be performed within the next few days.

DR. JOSEPH C. JAUDON.—I think this case emphasizes the importance of routine blood pressure determinations in the pediatrician's examination. Dr. Koerner first saw this child, and he felt, as I did later, that the child had evidence of constriction of the aorta. It was quite evident from the blood pressure readings that the major flow of blood from the heart was directed to the right side of the neck. The child's heart seems to be perfectly normal in size, and the heart tones are good. Growth and development have been unusually good. We felt that this was the type of thing on which we could deliberate and determine as accurately as possible the site of the coarctation. Accordingly, I asked Dr. Carson to do angiograms, and he has some beautiful films to show you. Dr.

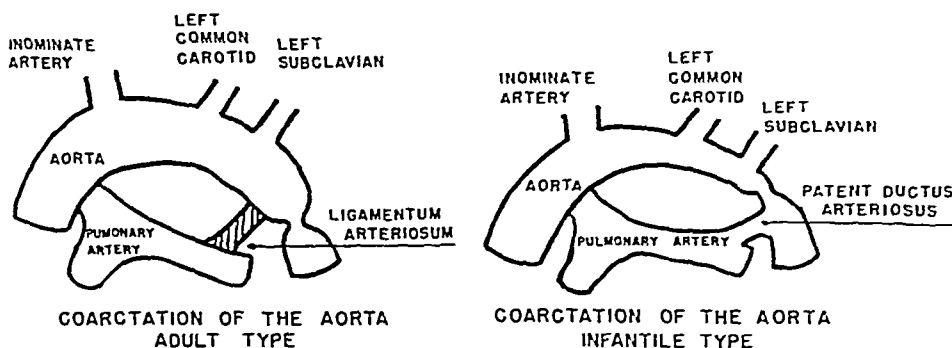


Fig. 19.—Diagrammatic illustration of adult and infantile types of coarctation of the aorta.

Burford has also been consulted, and after an extensive work-up by Drs. Carson, Goldman, and Burford, we have decided that an operation should be performed in the near future. Dr. Carson will show you that there is evidence of abrupt constriction of the aorta. It is very difficult to know what lies distal to the constriction: whether there is a normal descending aorta, and whether or not anastomosis can be performed. That can be shown only at operation. If the surgeons are unable to do an anastomosis, perhaps it will be possible to use one of the great vessels to by-pass the coarcted area. All of us are agreed that if the hypertension continues over a period of years, the boy's outlook is unfavorable.

DR. MERL J. CARSON.—This case illustrates the fact that children and young adults with coarctation of the aorta frequently do not exhibit any classical evidence of heart disease until a fatal cerebral hemorrhage or cardiac failure occurs. The importance of visualizing or otherwise localizing the point and type of coarctation which this child has is evident, I think, from an examination of Fig. 19.

There are two types of coarctation, which have been designated in the past as (1) the adult type and (2) the infantile. These designations have little to do with the age of the patient but are terms to designate different types of constriction. In the adult type of coarctation the constriction is a very sharp one, localized to a short area at or distal to the entrance of the ductus arteriosus into the aorta. In the infantile type of coarctation of the aorta the constriction is not a sharply localized one but is a general narrowing or constriction which may involve several centimeters of the aorta, often with a final terminal narrowing. In this type of coarctation the ductus arteriosus usually opens into the aorta at a point beyond the distal end of the constriction. Usually in the infantile type, the ductus is patent in the children who survive and remains so.



Fig. 20.—Roentgenogram showing notching of the ribs, from an older patient with coarctation of the aorta.

In considering this patient there were several things which made us think that he probably had the second, or infantile, type of constriction. We did not feel that he had a patent ductus arteriosus, but we did feel he had a diffuse, narrow, and long type of constriction of the aorta, for the following reasons: He had hypertension in the right arm with forceful pulsations in the radial and carotid arteries; the left carotid and left radial pulsations, were, however, extremely poor, so that we felt that the point of constriction was probably a diffuse one involving the orifices of these two vessels. In an effort to establish this point angiograms were made.

The x-ray diagnosis of coarctation of the aorta may be extremely difficult unless specialized methods of investigation are employed. A plain film in the

posteroanterior view usually does not show very much of value in a child of this age. In the older age groups there may be the typical notching of the ribs due to dilatation of the internal mammary arteries. This is not seen here.

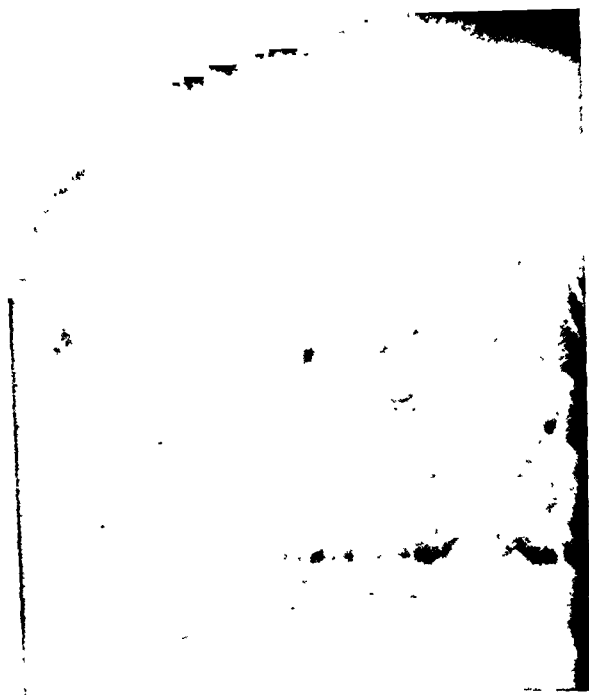


Fig. 21.—Showing abrupt constriction of aorta, beyond which Diodrast did not pass.

Such notching of the ribs is seen in the roentgenogram (Fig. 20) which was obtained in the case of an older patient who had coarctation of the aorta. The size of the heart is usually not remarkable in a child who does not have cardiac failure. Sometimes there may be evidence of dilatation of the ascending portion of the aorta, but this child does not show it. Occasionally, with the patient in the left anterior oblique position, an area of radiolucency which is visualized just posterior to the heart indicates that the aorta is very small. On fluoroscopic examination of this child we found no evidence of marked clearness of that area. Angiograms were then made. A No. 9 catheter was inserted into the right brachial vein up to the region of the superior vena cava, and 30 c.c. of 70 per cent Diodrast was injected as rapidly as possible. Films were taken at the rate of ten films every twelve seconds. The Diodrast was visualized entering the superior vena cava and then progressing to the right auricle and to the right ventricle. The pulmonary artery was well visualized. The pulmonary vein carrying blood from the lung into the left auricle was also delineated. The next film appeared to show an abrupt constriction of the aorta beyond which dye did not pass (Fig. 21). Unfortunately, at that moment the child became quite active and moved so that the most important films in the series were spoiled because of motion. In spite of the motion of the child a

broad aorta is well visualized, and the width of the aorta seems to be constant without evidence of narrowing in the ascending portion. It seems to be cut off very sharply at a point which appears to be at the first portion of the aortic arch.

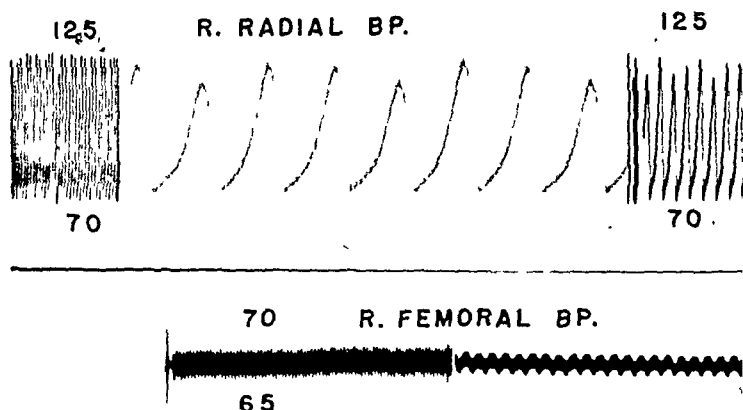


Fig. 22.—Demonstration of reduced systolic pressure in right femoral artery as compared to right radial artery.

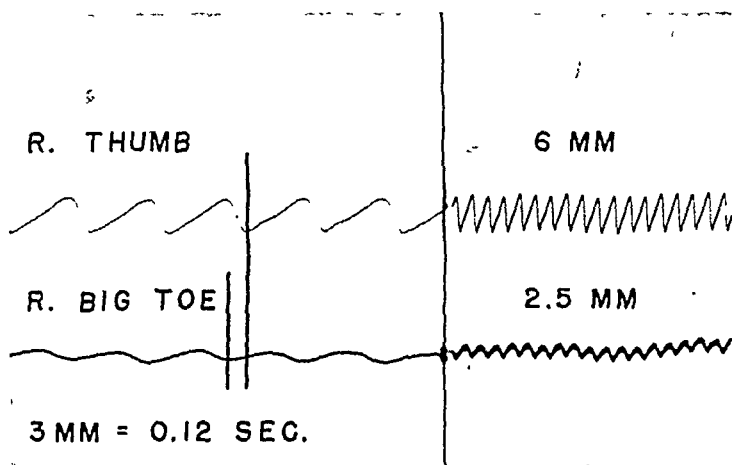


Fig. 23.—Demonstration of reduced blood flow in right big toe as compared to right thumb.

We felt, therefore, from examination of these films and from discussions among ourselves and with the radiologists that there was in this child sufficient evidence of a broad aorta without a generalized narrowing and with a rather sharp point of constriction, to justify an exploratory thoracotomy in order, if possible, to remove the point of constriction.

There are two methods by which one can relieve the effects of coarctation of the aorta. In one, a vessel arising proximal to the point of constriction is brought down and attached to the aorta below the point of constriction. That

may be accomplished with the subclavian or common carotid artery. In this case it obviously would have no value since very little blood is carried by those two vessels. Workers who have had experience with this procedure do not feel that it is of great value in relieving the hypertension associated with the coarctation, and relief of hypertension is of paramount importance in these

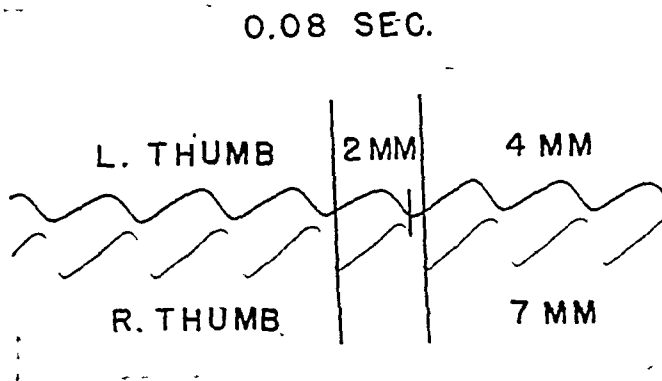


Fig. 24.—Demonstration of reduced blood flow in left arm as compared to right.

cases. The other procedure is that of excision of the coarcted segment followed by an end-to-end anastomosis of the cut ends of the vessel. That is the procedure of choice, and it is the one we would like to employ on this child if his coarcted segment is not too long, so that the ends can be closely approximated after excision of the stenotic portion of the vessel.

DR. MELVIN L. GOLDMAN.—I might say a word about the instruments used in carrying out this study. We did direct arterial punctures of the right radial artery and the right femoral artery and recorded the blood pressure directly onto a photokymograph camera using a Hamilton manometer. We also employed photoelectric cells for measuring the pulsations in the various extremities. The right femoral artery blood pressure was 70/65. We were quite sure we were in the femoral artery for two reasons: (1) The beat form is a 2-1, 2-1 pattern, and this pattern is repeated in the tracings of the blood pressure in the radial artery; (2) the diastolic pressure was 65 in the femoral artery, and the blood pressure in the right radial artery was 125/70, there being a marked diminution in systolic pressure between upper and lower extremities (Fig. 22). Additional blood flow studies in the extremities were carried out, comparing the upper and lower extremities, right and left fingers, etc. In the record of the right thumb and the right big toe (Fig. 23), the calibration of the instrument is such that if blood flow from these two extremities is equal, the amplitude of the records is the same. There was a difference in amplitude, indicating that the right thumb carries much more blood than the right great toe. There is also a delay in filling of 0.12 second between the right thumb and right toe. Ordinarily, there is only a very slight difference in filling between the upper and lower extremities, but in this instance there is something in

between the two which is delaying filling in the lower extremities. We then compared the right and left thumb, which again revealed the blood flow in the left arm reduced as compared with the right arm (Fig. 24). The most striking evidence of this is seen when the ear lobe is compared with the scrotum. We have made previous comparisons of these pulsations, and find it one of the best ways of showing differences in blood supply. The blood supply to the scrotum is mainly from the external pudendal artery, which comes off the femoral. The record shows a marked diminution in blood going to the scrotum as compared to blood flow to the right ear. Ordinarily, these should be about equal. With these findings, then we can also offer corroboration for the fact that the coarctation is proximal to the origin of the left subclavian artery.

Psychologic Aspects of Pediatrics

MANAGEMENT OF THE CHILD WITH MENTAL DEFICIENCY

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THE term mental deficiency is applied to the group of children, comprising about 2 per cent of the general population, whose mental development is of such a low order that they are unable to compete adequately with their peers. All degrees of deficiency are encountered, from the severely retarded children with congenital cerebral defects, whose unusual appearance and behavior can, as a rule, be recognized even by the inexperienced, to the morons, who may readily escape recognition unless their development and performance are carefully weighed.

In general, physicians are unduly pessimistic about the future of the mental defective. It is true that little can be expected from the idiots, imbeciles, and low-grade morons, most of whom die early in life. But many of the higher grade morons, who constitute the majority of mental defectives, are capable of making satisfactory adjustments in life and supporting themselves and their families. There are many jobs to be done in an organized society which the normally intelligent find uninteresting and perhaps degrading but which those of duller intelligence perform satisfactorily and contentedly.

Fairbank¹ gave a most illuminating report on the progress of 166 feeble-minded children, who had been found, in 1914, to have intelligence quotients between 61 and 72. It was prophesied at that time² that these children were liable "to recruit the ranks of vagrancy, alcoholism, prostitution, delinquency and chronic dependence, reproducing without care and handing over to others their defective offspring." Quite a different picture was found seventeen years later, in 1931, when 122 of these individuals, fifty girls and seventy-two boys, were re-examined. Only four had illegitimate children, eight had a history of chronic alcoholism, five had court records after they reached adulthood, and nine were being assisted by relief agencies before the depression. Ninety-five families out of 122 were financially independent, and thirty-six families owned or were buying their own homes. These men and women were employed principally as domestic workers and as unskilled laborers in factories, railroad and shipyards. Ten were skilled laborers and six were clerks. Forty individuals were available for retesting, and in all instances the mental age had remained practically unchanged during the seventeen-year interval. Fifty of their children, all of school age, were given intelligence tests. Of these, three had I. Q.'s under 70, four I. Q.'s over 120, and the rest gave I. Q.'s between 90 and 110.

¹From the Department of Pediatrics, New York University College of Medicine.

Similarly favorable results can be expected in the management of the moron if the parents can be made to appreciate and accept the child's handicap. They will then cease shopping around for panaceas and therapeutic short cuts and will, instead, expend their efforts and resources on training the child in accordance with his limited capabilities.

INFORMING THE PARENTS^{3, 4}

Informing parents that their child is mentally deficient is one of the least pleasant tasks which the physician is called upon to perform. The tragic news that the mentality of their child is hopelessly impaired is to many parents a verdict worse than death itself.

Before discussing the matter with the parents, a complete history should be taken and a careful examination made. Even though the child's condition may be evident at a glance, the parents should be made to feel that every conceivable detail has been considered before a judgment is made.

The opinion given should be frank, honest, and unequivocal, but should be couched in terms which do not offend the parents. Such words as idiot, imbecile, moron, subnormal, defective, mongol, and cretin are to be avoided. The parents may be told that the child is slow or retarded in development, and it should be made clear at once that he will never catch up with normal children and will never be as bright as other children. The child will learn but always at a slower pace than the normal child, never attaining normal ability even in adult life. If the parents are not told specifically that the child will continue to develop, slow though his progress may be, they will be falsely encouraged when he starts to walk and talk, etc., and they will be resentful toward the physician whose prognosis has, in their opinion, been unduly pessimistic.

In many instances the parents, before coming to the physician, have been told that the child is abnormal or have themselves suspected it. These cases are generally easy to manage and simply require confirmation. If the parents are not aware of the difficulty, or if they choose to conceal their knowledge or suspicions, seeking an opinion unbiased by a previous diagnosis, the situation requires more delicacy.

The parents may sense what is in the physician's mind from the character of the questions regarding the child's development and from questions such as: "Is he behaving like your other children when they were his age or like your friends' children?" After the history and examination have been completed, one may ask whether the parents have noticed that the child plays differently from other children or whether they have not been impressed with his slowness in catching on to things. The mother will usually reply that the child is slower in general, and then may go on to tell how good is his memory for tunes or for faces or how wonderful is his sense of rhythm. The physician will do well to listen patiently to these words while the parents are bracing themselves for a verdict which they are now prepared to receive.

The parents will want to know whether the diagnosis is certain. When the diagnosis is straightforward and definite, as in the case of mongolism, the examiner should say so. But it is well to keep in mind that, among others, conditions such as congenital athetosis, hydrocephalus even of moderate degree, and late development of speech are compatible with normal mentality. Schizophrenia, especially in the young child, may be readily confused with mental deficiency. We may, therefore, properly give the parents some comfort by saying that, though the diagnosis is justifiable on the basis of past experience and present knowledge, mistakes have been made.

In reply to questions regarding the cause of the defect we can only say that, with rare exceptions, it is unknown. Parents will often mention some distant relative who is afflicted with a mental disease, but this may be dismissed with the statement that mental disease is unfortunately so common that there is hardly a family without a victim. The physician should make a special effort to avoid having the parents blame themselves or one another for the child's difficulty.

A matter of great concern to the parents is how far the child will develop. Will he learn to walk, talk, go to school, earn a living? A fairly accurate prediction can be made if the child is old enough to take a mental test. The idiot, whose mentality does not exceed 15 per cent of normal (intelligence quotient 15 or less), may learn to walk and say a few words but nothing more. The imbecile, whose mental range is between 15 and 45, will learn to walk and talk and take care of his personal needs, but he will not be able to go to school or earn a living. The moron makes up the largest proportion of mental defectives. The intelligence range in this group is fairly wide, from 45 to 70, and achievement varies with the intellectual capacity. The lower grade morons achieve little more than the imbeciles, but those with intelligence quotients between 60 and 70 will be able to attend school although they will either be below the proper grade for their age or be in the ungraded class. They may be able to support themselves by manual labor or in certain occupations if there is adequate supervision.

The intelligence quotient is a fairly good yardstick for predicting the rate of progress. For example, a child whose I. Q. is 50 will advance at about 50 per cent of normal and will require about two years to learn what a normal child learns in one. In addition, the intelligence quotient gives information regarding the limit of mental growth. The child whose intelligence quotient is 50 will attain, when his mental growth is complete, a mentality corresponding to that of a 6- to 7-year-old child. Mental growth is completed during adolescence as in the case of the normal child. It is important to keep in mind that, though the mentality of the feeble-minded adult may be only that of a 7-year-old child, he will, through the years, have had many more experiences and he will have acquired much more information than the child of similar mental capacity.

Parents may find consolation in the knowledge that the child himself will not be unhappy because of his handicap. Defective children, especially those of a low grade of intelligence, appear unaware of their mental shortcomings and seem to enjoy life more than those with good mentality.

Whether the parents ask about it or not, the advisability of having more children should be discussed. With the exception of certain of the congenital cerebral defects which are known to be familial, such as encephalitis periaxialis diffusa and phenylpyruvic oligophrenia, they can be assured that there is no more danger in their subsequent children being defective than other people's. In the case of mongolism, subsequent children are, with rare exceptions, normal.

Amaurotic family idiocy is a special case. The parents should know that the probability of further children suffering from the same defect is high. Nevertheless there are many instances where other children were entirely normal, and it has therefore been our practice to advise parents to try a second pregnancy. It may help to point out that, should a second child be affected, the episode will be terminated before the child is 2 years old. If there have been two affected children in the family, the parents should be advised against trying again. When the parents are unwilling to go through another pregnancy, artificial insemination may be suggested. The frequency with which amaurotic family idiocy occurs in consanguineous marriages indicates that the trait is probably transmitted by both parents.

IDIOTS AND IMBECILES

Management of the mentally retarded child depends on the degree of defect. Little can be done for idiots. They should be given adequate medical care either at home or in an institution. When the condition is recognized at birth, as in the case of mongolism, breast feeding should be discouraged in an effort to lessen the emotional attachment of the mother for the child.

At I. Q. levels between 20 and 40 the child may be taught specific habits appropriate to his intelligence. Even the imbecile can learn cleanliness, proper ways of feeding himself, obedience, and the performance of simple tasks, though he is apt to need constant reminding. He can learn his name and per-haps where he lives. Institutional care is to be recommended in most instances.

MORONS .

A program for the management of the moron should have as its aims the following:

1. Training of the child within the limits of his mental capacities.
2. Correction of physical defects.
3. Prevention and correction of emotional problems.

The child should be drilled in the care of his body and in the social amenities, since a well-appearing, well-mannered individual will make a better impression than a crude, untidy one. Training must be specific, as the mental

defective cannot grasp generalities about the need for proper hygiene. Each activity—washing, bathing, brushing teeth, attention to clothes and hair, etc.—must be taught as a special habit.

Feeble-minded children may be taught to listen rather than to enter a general conversation, to speak only when spoken to, and then to reply briefly. This is not unkind, since they are quickly confused when talking, they say stupid things, and become embarrassed.

Academic training will be necessarily limited, but, whenever possible, the child should be taught simple counting, recognition of numbers, making change, telling time, the days of the week, and the months. He should be able to read signs and newspapers and to write his name.

At 6 years of age, society expects that a child will go to school, regardless of the status of his mentality. Children with I. Q.'s between 50 and 70 should be placed in special classes, at least for trial periods. Though a child with an I. Q. of less than 50 will occasionally profit by school, this is generally considered the lower limit of educability.

Education for the feeble-minded should have as its aims training for a vocation and training for leisure-time activity. Berry⁶ has pointed out that, since about 20 per cent of the adult population are engaged in unskilled labor, it is folly to attempt to prepare children of inferior intelligence for skilled work. They should, instead, be prepared to become law-abiding, self-supporting citizens in the simplest occupations.

Among the possible leisure-time activities for the subnormal child are music, athletics, handicraft, and group games.

Socially desirable traits, such as honesty, willingness, loyalty, patience, and courtesy, are perhaps even more necessary with this group than with normal individuals, since in many situations it is preferable to have a person who is reliable, pleasant, and courteous, even though dull, than vice versa.

Physical defects and undesirable habits should be corrected whenever possible. Impurities of speech, strabismus, awkward gait, and dental defects are common among the feeble-minded. Not only is the child more presentable but he is less likely to be less self-conscious and embarrassed if his appearance is agreeable.

The successful management of the feeble-minded child depends to a large extent on the avoidance of emotional problems. There is reason to believe that, in some children who are mentally defective by reason of gross damage to the brain, the cerebral lesion may also lead to undesirable behavior, especially restlessness, distractibility, and hyperexcitability. But, in the large majority of afflicted children, problems arise as a result of parental mismanagement.

Certain errors are commonly made by the parents of feeble-minded children. These errors are difficult to avoid, but they are even more difficult to correct once parental attitudes have become established.

Ideally, the defective child should have his share of the parents' affection and attention—no more nor less. Unfortunately this is rarely the case. Usually he gets more than his share, occasionally less. During the first few years of life the parents, particularly the mother, sensing the child's weakness, tend to overprotect and overserve him. A sense of guilt often accompanies the overprotective attitude, and the mother may center all her attention and affection on the child in an effort to make up to him for the harm she thinks she has done to him in bearing a defective child. She continues to do things for the child which he, belatedly it is true, is ready to do for himself. The defective child of 5 years, with an intelligence quotient of 60, cannot be expected to perform like children of his chronologic age, but he should be expected to do the things a 3-year-old can do and to behave accordingly. This exaggerated attention prevents the mother from giving her time to other members of the family. In addition, the parents may feel ashamed and, for this reason, limit their social activities, thus intensifying their own personality problems.

Such overindulgence is extremely common, and it often creates a more serious obstacle to adjustment than the retardation itself. Most parents can curb their overprotecting attitude if it is pointed out that, in this way, they are adding still another handicap to the one already present.

As the child grows older and his mental inadequacies become more apparent, the parents often come to feel resentful toward him. They are annoyed with his slowness in learning, his awkwardness, and his unattractive appearance. Moreover, as a result of their overindulgent behavior toward him, he may now be a spoiled as well as a mentally retarded child. The moron, although less sensitive to parental attitudes than the normal child, nevertheless does sense the critical attitude of his parents, especially as in his case they are likely to be outspoken in their criticism.

If he is expected to compete at school with normal children, his emotional discomfort will be increased. Unable to comprehend what is going on in the classroom, he is restive and often upsets the class routine by clowning. Bad reports from school add to the parental dissatisfaction. The behavior of the emotionally disturbed defective pupil is characterized by hypermotility and restlessness.

The parents need to be continually reminded of the intellectual shortcomings of the child. If they can afford it, they will do well to enter him at a special school where he will be free from the competition with normal children and where he may receive training suitable to his ability.

INSTITUTIONAL CARE

Institutional care should be recommended for severely defective children when they interfere with normal family life. If the defective child remains at home the mother may become unduly attached to him to the exclusion of the normal siblings, and she may be unwilling to have more children because she feels that he needs all of her attention. The siblings are ashamed and refuse

to have guests in the home. On the other hand, in special situations as, for example, when the afflicted child is the only one in the family and the parents refuse to have more children or when the child is much younger than the other siblings, the parents may find a certain amount of companionship from having him with them.

Institutional care is also indicated for defective children who show anti-social behavior.

Higher grade defectives, during the adolescent years, will generally benefit by a period of institutionalization. Here, protected from competition with normal children, they can be trained to a job and to social living. Moreover, they are sheltered during the years of rapid sex maturation when they are likely to get into difficulties if unsupervised. This is especially true of the girls.

Segregation accomplishes three things: It protects the family unit, it protects society against the easily misled defective, and it is a method of training the individual to occupy a place in society.

The term "institution" carries a certain stigma, and it is therefore wise to speak of a "training school." Some of the private institutions are called "schools for exceptional children."

In general, the children adjust quickly to the institution and are happy there. It offers companionship with children of their own ilk, freedom from the close supervision necessary at home, and relief from the strain of trying to compete with mentally normal children. There is little formal teaching in most of these schools, but they give good general care, athletics, training in simple tasks, and an opportunity to experience social living.

Glutamic Acid.—Though glutamic acid has been shown to increase intellectual capacity appreciably, it is not yet clear how much practical value can be expected from its use. It would appear to be most valuable in the moron in whom an improvement in mental performance is encouraging to both child and parents.

Benzedrine is of no value in increasing mental capacity.

Families with a mentally defective child will do well to live in a rural area where competition for the child will not be so great as in a large city, and where he is more likely to be accepted and helped by the community.

MONGOLISM

Mongolism is the most frequent type of mental deficiency recognizable during early life. It is estimated that between 0.2 and 0.3 per cent of all births are Mongols. This means that between 6,000 and 7,000 are born each year in the United States.

The father should be informed as soon as the diagnosis is made, and he should be consulted about telling the mother. In most instances it is wise to advise him to tell his wife of the baby's condition; otherwise she may later on consider that the father and the physician have entered a sort of conspiracy from which she has been excluded.

Though Mongols generally attain a mentality corresponding only to that of a 2- to 4-year-old child, the number who reach a mental level of 6 to 10 years is appreciable. Pototzky and Grigg,⁸ in a study of a selected group of twenty-one Mongolians at a private school, found that eleven had mental ages above 6 years; two of these displayed borderline intelligence (mental ages above 10 years). An interesting feature of the study was the observation that the "social age," which is a measure of social adaptability, was higher than the mental age to a greater degree than among other mental defectives. Some Mongols may be taught to do simple housework, gardening, and general handy work. They are gentle, lovable and easily manageable, though inclined to be stubborn. As adults they show little heterosexual interest, and hence there is little danger of their getting into sex difficulties. The more severely defective ones die in early life from infections and the frequently associated cardiac defects, but the brighter ones tend to survive longer, often into adult life.

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Comments on Current Literature

STREPTOMYCIN

A RECENT issue of the *Journal of Laboratory and Clinical Medicine* carries a report by Major Edwin J. Pulaski and Colonel Sam F. Seeley¹ describing cumulative experiences with streptomycin therapy in the United States Army Hospitals, Halloran General and Brooke General. This report presents their observations in summary form, and is based on an analysis of 1,200 cases.

Of special interest is the series of 465 patients with infections of the urinary tract, all of whom had complete bacteriologic survey of the urine before treatment. Seventy-nine per cent of the micro-organisms isolated were gram-negative bacilli. Of the remaining 21 per cent, which were gram-positive cocci, one-third were nonhemolytic streptococci. Extensive culture sensitivity studies revealed that streptomycin exerted a bacteriostatic effect in vitro on 87 per cent of the bacteria recovered before treatment and that 13 per cent were naturally drug-fast.

In correlating the laboratory findings with the clinical response to therapy, the authors conclude that "if bacteria are not inhibited in vitro by a concentration of 16 μ g. per cubic centimeter, the chances of eliminating them by streptomycin therapy are not good." Since the drug is excreted in very high concentration in the urine (1,000 μ g. per cubic centimeter, or more), failure of response, according to the authors, "suggests that streptomycin acts primarily through delivery by way of the blood stream to the tissues and not through the urine." Therapy resulted in cure in 34 per cent of the patients treated, improvement in 21 per cent but without complete bacteriologic remission, and in no beneficial effect in 45 per cent. Failures were most common when the infectious agent was *Pseudomonas aeruginosa* or *Streptococcus faecalis*. While many factors entered into failure of therapy, drug-fastness is believed to be a constant feature in cases where the urine was not sterilized by the prescribed course of treatment. Administration of a second course of therapy did not seem to give better results than did the first course. Local instillation of streptomycin in the genitourinary tract seemed of little value.

Ten patients with tularemia were treated with streptomycin, one oculo-glandular type, one typhoidal, and the others ulceroglandular. Streptomycin, administered intramuscularly in daily dose of 2 Gm. for a period of seven to fourteen days, resulted in recovery in all patients without relapse or complication. As Pulaski and Seeley state, their experiences support the conclusions of others that streptomycin is the most effective agent now available for the treatment of tularemia.

In the treatment of infection involving the central nervous system, the results obtained were similar to those reported by other authors. The need for intrathecal administration combined with the intramuscular route was emphasized.

Twenty-nine patients with brucellosis were treated with streptomycin; sixteen of these were considered to have acute cases and thirteen were considered chronic. Blood cultures were positive for brucella in fourteen of the sixteen patients with acute brucellosis, and bacteremia was demonstrated in two of the chronic cases. All strains of brucella isolated were sensitive to streptomycin in vitro. The dosage of streptomycin varied between 1 and 2 Gm. daily, and in two patients was 6 Gm. daily, for an average period of fourteen days. None of the

patients with chronic brucellosis derived any benefit whatsoever from streptomycin therapy. Of the patients with acute brucellosis, only two of the twelve treated with streptomycin alone had fairly prompt remission and negative blood cultures. Exacerbations occurred in five of the twelve patients. It was the clinical impression of the authors that the foci of infection in brucellosis were not penetrated by streptomycin administered parenterally. Oral sulfadiazine added to parenteral streptomycin therapy produced favorable response in two of five patients treated in this manner.

In this connection it is interesting to point out that Howe and Heyl² in the *New England Journal of Medicine* report the successful therapy of an acute case of brucellosis in a 52-year-old woman. These authors re-emphasize the concept of Meyer³ that the selective intracellular parasitism in mesenchyme cells of various organs is of greatest significance in the pathogenesis of brucella infections. Howe and Heyl suggest the administration of relatively large doses of streptomycin, since in sufficiently high blood concentration maintained for adequate periods, streptomycin exerts bacteriostatic or bacteriocidal action on intracellular organisms. In their patient, a 52-year-old adult, Howe and Heyl succeeded in obtaining blood levels of streptomycin varying between 20 and 25 μ g. per cubic centimeter of blood, by giving 6 Gm. daily, one gram every four hours over a period of ten days. In reviewing the literature, these authors gained the general impression that patients in whom the highest blood levels of drug were maintained for even relatively short periods, showed signs of better response than those in whom lower levels were maintained over relatively longer periods. Such intensive therapy, however, is not without hazard.

Another interesting section of the Pulaski and Seeley report concerns their experiences with infections of intestinal origin. Six patients with typhoid fever were treated, and no remarkable results were achieved. However, in the case of one 5-year-old child who was given the usual adult dose, the fever dropped abruptly, which suggested response to streptomycin therapy. It is possible that in typhoid fever, intensive therapy over a short time might give results comparable to those achieved with brucellosis.

Beneficial effects were noted in bacillary dysentery caused by *Shigella sonnei* and *Shigella flexneri*. The most striking results were noted in patients during the first attack of illness. Three infants with diarrhea due to salmonella responded favorably to oral streptomycin (100 mg. per kilogram daily for four to seven days). In thirteen cases of epidemic diarrhea of unknown etiology, oral streptomycin therapy in a dosage of 0.1 Gm. per pound per day was given in the milk. In addition to the routine measures employed in the therapy of infantile diarrhea, it was the impression of the authors that streptomycin was the determining factor in saving at least four of the ten survivors.

Pulaski and Seeley also summarize their experiences with streptomycin in the treatment of bacteremia, peritonitis, wound infection, and tuberculosis.

One section of the report is devoted to the incidence of untoward reactions, and the case records of 1,153 patients are reviewed and tabulated. The over-all incidence of side effects was 27.9 per cent (322 patients). Since this series was begun in 1945 when streptomycin was relatively impure, it is believed that a number of the side reactions might have been due to impurities in the streptomycin rather than to the streptomycin molecule itself.

Neurological disturbances were the most important, and two types were noted: the persistent, slowly regressing type, and the transient type. The transient reactions, which include circumoral pallor and tingling of the face and extremities, were observed fifty times and appeared as early as following the first intramuscular injection. Tinnitus, which also appeared early, was noted in twenty-eight patients. Vertigo may be either transient or persistent, and

its appearance should be reason for caution. Transient vertigo, which appeared between the third and the tenth days of treatment, was recorded thirty times, a probable underestimation of the incidence. Persistent vertigo, accompanied by ataxic gait and absence of vestibular response to caloric tests, was noted in fifty-six patients (5 per cent). It is important to point out that all patients with persistent vertigo received therapy for a period of from twenty-one to 120 days, the incidence of this reaction being highest in those treated for 120 days. The earliest appearance of the disturbance was recorded in a patient receiving 3 Gm. of streptomycin daily for fourteen days. Partial deafness was recorded in twelve patients (1 per cent). All were patients with tuberculosis on the 120-day program.

Dermatoses which were accompanied by pruritis, usually with fever and eosinophilia, occurred in thirty-five patients. These sensitization reactions usually occurred between the fifth and tenth days of therapy. Withdrawal of the drug always resulted in subsidence, and reappearance did not always follow a second course. In some patients the reaction gradually disappeared in the face of continued streptomycin administration. Antihistamine drug therapy was used in conjunction with streptomycin.

There were four instances of exfoliative dermatitis, all in patients with tuberculosis. The reaction is serious and requires prompt withdrawal of the drug. Disappearance of the dermatitis is gradual.

In summarizing their experiences, Pulaski and Seeley emphasize the wide variation in streptomycin sensitivity among the bacterial species, and urge that wherever possible susceptibility of the organism be checked by the laboratory prior to therapy. Indications for streptomycin therapy include: urinary tract infections with gram-negative organisms, tularemia, bacteremia, pneumonia, and meningitis due to susceptible organisms, certain otolaryngologic conditions associated with gram-negative bacteria, and possibly bacillary dysentery and salmonella infection. Acute brucellosis with bacteremia responded favorably to streptomycin therapy, especially when given in combination with sulfadiazine. It is the opinion of Pulaski and Seeley that in spite of the incidence and the type of untoward reactions, the toxicity of presently available streptomycin is sufficiently low to justify its use in serious infection against which it has been shown to be effective.

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News and Notes

The American Board of Pediatrics announces the appointment of Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa., as Executive Secretary, effective May 1, 1948. After that date, all official communications should be addressed to Dr. Mitchell.

Work with the children began in February on the St. Louis study to evaluate vision-testing procedures suitable for elementary school children. The study is sponsored by the National Society for the Prevention of Blindness, the F. S. A., and the Public Health Division of the State of Missouri. Tests are being carried out with the Massachusetts Vision Test Equipment, the American Optical Company Sight-Screener, the Bausch and Lomb Ortho-Rater, and the Keystone Telebinocular. In addition, each child will be given a thorough eye examination including refraction under cycloplegia, at the eye clinic of the Washington University Medical School.

Between 500 and 600 children in the first and in the sixth grades are being tested. Dr. William L. Benedict of Rochester, Minn., is chairman of an ophthalmologic advisory committee, and Dr. Richard Scobee of Washington University will have ophthalmologic supervision of the study.

Each set of tests will be made independently, and results will go to a statistical committee for analysis, headed by Earl L. Green of Ohio State University as chairman. It will take approximately a year to complete the field studies, after which the statistical analysis will start.

The American Academy for Cerebral Palsy will hold its first annual meeting in Baltimore, on May 30 and 31, 1948.

Dr. Charles Bradley has been appointed associate professor of pediatrics and psychiatry on a full-time basis at the University of Oregon Medical School.

Dr. Alfred Vignee has been appointed clinical professor of pediatrics at the New York University College of Medicine.

The International Society of Hematology will hold its bi-annual meeting at the Hotel Statler in Buffalo, New York, Aug. 23 through 26, 1948.

The following time has been tentatively allotted for symposia and presentations: one-half day on general subjects, including radioactive and stable isotopes in hematology; one-half day for problems and diseases related to the red cells; one-half day for problems and diseases related to white cells; one day for immunohematology, Rh-Hr (CDE-cde) antigens and antibodies, and hemolytic anemias; one-half day for coagulation problems and hemorrhagic diseases; and one-half day for business meeting.

Book Reviews

Endocrine Therapy in General Practice. Elmer L. Sevringhaus, M.D., ed. 6, Chicago, 1948, Year Book Publishers, pp. 264. Price \$4.00.

An extensive revision of the fifth edition, published in 1945. This is an excellent book for the man in practice as it discusses in a direct way the use of endocrine products in therapy and their limitations. No small part of its value and usefulness lies in the fact that it is based on the extensive experience of the author, and is not a compilation from the literature. The approach throughout, of which the chapter on the endocrinopathies of children and adolescents is an excellent example, is unusually sane in the confused field of endocrinology.

Nursing in Modern Society. Mary E. Chayer, R.N., M.A., New York, 1947, G. F. Putnam's Sons, pp. 289. Price \$4.00.

This book is addressed primarily to nurses and attempts to present nursing in relation to social forces. The author states a revolution is needed in nursing, and that one is being experienced. It is of value, therefore, to review the book more in detail, as it presents the ideas and attitudes of a leader in nursing education, who holds the position of associate professor of nursing at Columbia.

The theme is that nursing of the future will be an important aspect of our social structure, and the place of the nurse must be defined within the larger pattern of community life. According to the author's viewpoint, the nurse of the future should be a superindividual educated in teaching, psychology, economics, child development, geriatrics, health education, and the social sciences, who in some way will bring help to a chaotic world. All this is to be brought about by more and more education of the nurse.

Quite unwittingly the author has presented a text which explains to considerable extent why nursing is in a "critical state" at present and why the public is demanding changes in the nursing profession. The primary function of the nurse, like that of the doctor, is the care of the sick. This is what the public asks and demands of the nurse despite the efforts of a group of nurse educators, which Miss Chayer represents, to make something else of her. There is not the slightest recognition in the book that nursing is an ancillary branch of the medical profession. All of the fields of medical service which the author discusses, such as hospital care, child welfare, health education, industrial medicine, public health, and school hygiene, have been developed by the medical profession. They have not been pioneered or developed by the nursing profession but the nurse has been called into the picture as an important and necessary aid in carrying out techniques. The nursing contribution has been, is, and will undoubtedly continue to be, secondary.

We have no quarrel with the nurses, but we cannot help but feel that much of the trouble with the nursing situation is due to leadership which has directed nursing away from its primary purpose to one of higher education. We might put it this way—the text represents the thought of a group of nursing leaders who are far more interested in education than they are in nursing.

As all familiar with the nursing situation know, plans for the development of the training of practical nurses are being rapidly accelerated. The author proposes that only those be admitted to this "one year course or equivalent for the new supplementary group" who have the intelligence and education to enter on a longer training if they later so desire. The primary purpose of the training of these practical nurses is to meet the public need for someone to take care of the patient and not to recruit possible candidates for higher education.

We rejoice with the author that the training of nurses is no longer a method of obtaining cheap labor for the hospital. We believe there is a place for a limited number of schools of the university type for the education of those who will become teachers and administrators. The place and need for these, however, is limited in comparison with the need for nurses to care for the sick.

The author is best in her discussion of health education.

B. S. V.

Hearing and Deafness. A Guide for Laymen. Edited by Hallowell Davis, M.D., New York, 1947, Murray Hill Books, 496 pages. Price \$5.00.

This book on the problems of the deaf can well be recommended by the physician to patients who are facing deafness and to the parents of a deaf child. Under the editorship of Dr. Davis, who contributes a number of chapters, twelve experts in their own fields discuss in fairly nontechnical terms the various problems involved in deafness. In one section, hearing and hearing loss are discussed with chapters on the medical aspects and surgical treatment. In another section, of particular value to the lay reader, auditory tests and hearing aids and their choice are considered. The section on education and psychology is of particular interest to the pediatrician as it contains chapters on the hard-of-hearing child and the deaf child. Included among other subjects are rehabilitation, speech training, and vocational training for the deaf. It is an unusually complete discussion of the many aspects and the many problems of the deaf.

Baby Care From Birth to Birthday. E. G. Lawler, M.D., Chicago, 1947, Wilcox and Follett Co., pp. 496. Price \$5.00.

Another book for parents on the care of the baby with routine, generally accepted advice. The book differs from others in the same field by being most profusely illustrated. This is the reason undoubtedly why the price is much higher than that of most manuals of a similar nature. Some of the illustrations, as, for example, a picture of a baby suspended in a fracture cast, hardly seem germane to the subject. In the review copy, the paging of the Table of Contents does not correspond with the text.

Illustrative Electrocardiography. Julius Burstein, M.D., and Nathan Bloom, M.D., F.A.C.P., ed. 3, New York, 1948, D. Appleton-Century Co., pp. 309. Price \$6.00.

In this thorough revision of a popular textbook of electrocardiography, most recent advances in the subject have been included without detracting from the essentially simple and elementary character of the book. The fundamentals of electrocardiography are presented in a lucid and nontechnical manner and the normal electrocardiogram reviewed. There then follow brief descriptions and illustrations of various disturbances of rate and rhythm and a brief but concise review of the changes in myocardial infarction, ventricular strain, and in a variety of other conditions. The addition of sections on precordial leads and the phonocardiogram makes the book more complete than the previous edition, but a new section on the radiologic examination of the heart seems not only out of place but also rather incomplete. To the pediatrician, for example, the merest mention of anomalous vascular rings without an illustrative example appears to be inadequate coverage for one of the few congenital cardiovascular lesions amenable to surgery. The omission of a film illustrating patency of the ductus arteriosus and an inadequate and sometimes incorrect description of the findings in this condition seem to be more serious defects. Moreover, although the paper is adequate for reproduction of electrocardiographic tracings, the roentgenograms seem to be lacking in detail.

As a primer of electrocardiography, however, the book should fulfill its purpose of providing a readable, well-indexed, and adequately illustrated text for the more occasional electrocardiographer.

GOODFRIEND

Cardiopatías Congénitas de la Infancia. Dr. Agustín Castellanos y González, Havana, Cuba, 1948, M. V. Fresneda, pp. 406 and an atlas of 20 plates.

This monograph details Dr. Castellanos' interesting findings in congenital heart disease in infancy and childhood. It presents a brief but thorough review of the embryologic development of the mammalian cardiovascular system and then discusses the various methods of examination of the heart—electrocardiography, physical examination, cardiac catheterization, venogram, phonocardiogram, and various radiographic techniques. Interest will inevitably center, however, in the sections devoted to angiocardiology—an investigative method which Dr. Castellanos has long fostered and to which he has contributed much. The atlas of twenty plates which is appended to the text together with explanatory diagrams demonstrates the value of the technique and the information which it offers.

This book will doubtless be compared with Dr. Tausig's recent volume, *Congenital Malformations of the heart*. There is little basis for such a comparison. The latter volume presents a vast and detailed clinical experience which has utilized relatively few techniques, while the former is a discussion chiefly of possible modes of investigation with a minimum of documentation. Both seem to be required by the pediatrician interested in congenital anomalies of the heart.

GOODFRIEND

The Pathology of Nutritional Disease. Richard H. Follis, Jr., M.D., Springfield, Ill., 1947. Charles C Thomas, pp. 236. Price \$6.75.

This is an interesting and valuable book. It should be used by all physicians whose wish it is to be adequately informed concerning what was honestly known (in 1946) in the important, difficult, rapidly growing, and often irresponsibly handled field of nutritional diseases. Especially is such information desirable in "these days," as the author says, "of vitamin inflation."

Dr. Follis has ably assembled the (then) existent—more than a year, apparently, passed between completion and marketing of the book—body of knowledge concerning his subject. Only nutritional diseases in mammalia are considered. After a short section on Dietary Deficiencies in General, there follow parts on Essential Elements, Essential Amino Acids, The Fat and Water Soluble Vitamins, and The Essential Fatty Acids. A useful final section concerns the pathological anatomy of specific tissues, and is properly labelled "A Recapitulation and Comparison."

In the discussion of each essential substance, four subheadings exist: Historical, Biochemical Relationships, Pathological Effects, and Deficiency in Man. Proper space is well apportioned to these headings, and the text is, resultantly, enjoyable reading.

The illustrations are adequate, in quality and number. The bibliography is excellent for, among other considerations, its recency; three quarters of the publications cited appeared in the decade preceding the book's completion. In a field so recently developed as the modern study of dietary deficiencies, this consideration is more than ordinarily important.

All in all, the book is an excellent critical review of the field, lucidly and compactly presented. The volume is attractively set up. One further considerable service is the repeated indication of avenues for further investigation. Lest anyone feel complacent with the results of past researches, it is offered that "it must be emphasized that no single nutrient has been simultaneously studied from the biochemical, physiological and morphological standpoints." The further sad truth is noted that in only too many past projects, inadequate pathology (or none at all) accompanied otherwise good studies.

A large number of typographical errors and slips-of-the-pen occur. These include errors in spelling, page indexing, reference numbers, and even word-switches (e. g., hypophysis for hypothesis, p. 67). While trivial, such flaws molest the reader; one hopes that corrections will be made in the future.

J. B. F.

Editor's Column

FEDERAL AID FOR EDUCATION IN PEDIATRICS

The proposal of the *Committee for the Improvement of Child Health* that federal aid should be sought to improve pediatric teaching in the medical schools is bound to lead to an animated discussion which will not be limited to the pediatricians. Because of its broad significance it is of importance to physicians in general, and in particular to those who are responsible for the conduct of our medical schools. It is not a new idea, and we have heard it discussed pro and con a number of times by medical educators. The fact that the concrete proposal comes not from the institutions and schools but from representatives of the physicians concerned with health of American children, adds a new slant to the idea.

We have contended for many years that improvement in medical care was dependent upon the training and education of those furnishing the care, and on facilities, rather than on the method of payment for the physicians' services. As this proposal expresses the considered judgment of an unusually able and representative group in whom we have the greatest confidence, and as it has as its objective the furthering and improving of the education and training of those upon whom the medical care of children depends, we find ourselves in sympathy with the proposal.

Tax aid for medical care is a well- and long-established principle. Further, a large part of our medical education is tax-supported, as many of our medical schools are parts of state universities where the high cost of medical education is in large part supplied from tax money. We know of no instance in which this has led to interference with the technical side of medical education as developed by the medical faculties, except for the limitations imposed by available funds.

* * *

The critical situation of our medical schools from the financial standpoint has been the subject of much discussion. Medical education is recognized as being the most costly form of education, and the costs have been rising out of proportion to the general increase in the cost of living and of education in general. Tuition fees, which meet about 30 per cent of the cost of educating a doctor, have been raised to a point which has resulted in an economic barrier to medicine as a career for many promising young men and women, as we pointed out in an editorial in the *JOURNAL* last October (31: 482, 1947). Increased tuition fees cannot be used as a further source of income. Income from endowment, which provides roughly about 35 per cent of the cost, has decreased with the general lowering of interest rates from those of a decade ago, and with our present tax structure endowments are becoming more and more difficult to obtain. The balance of the cost, some 35 per cent, must be obtained from some source of current revenue. A number of the medical schools, in order to make ends meet, have been considering the plan of the clinical teachers practicing medicine as a corporate group to obtain funds for the medical school. There are

very sound objections to this commercialization of our teaching institutions. There is seemingly left only current gifts and tax subsidies to meet the rising cost of medical education.

* * * *

But the proposal and recommendation of the Committee is somewhat different from a general federal subsidy for medical education. The federal government has appropriated \$18,500,000 for the current year for grants to states for maternal and child health services. Other bills are pending which propose further funds to meet certain existing health needs for children. Unless there is adequately trained personnel to carry out the proposed services it will be money largely wasted, as was the case with the huge federal expenditures under the E M I C program, although it may be argued that this was justified to support the morale of soldiers overseas. The child health survey shows wide variations in the distribution of medical personnel capable of carrying out the purposes of these federal appropriations. The Committee reasons, and we agree, that what is most needed is improved training in pediatrics, which is basically dependent upon the character and extent of the instruction in pediatrics in the medical school. Up to the present, federal expenditures for health services for children have to a large extent put the cart before the horse, so to speak.

* * * *

The Committee proposes a flat sum to be allocated to the pediatric departments of each medical school, on the condition that present funds are not cut. Further, an additional allocation will be made according to needs and student enrollment. The schools will use the money for teaching purposes according to the needs of the department. If in any school there is no need for funds, or fear of federal control, the matter can end right there, as there is no obligation for any school to accept a federal subsidy. For allotment to the pediatric departments, \$2,500,000 is suggested, which will mean something over \$30,000 per school. In addition an equal amount is proposed for fellowships, for educational extension work in the smaller communities without medical schools, and for grants-in-aid to states to provide trained pediatricians to work in areas or districts where they are not at present available. The Committee proposes that the control of the funds be put in the hands of a group of nine physicians appointed by the Federal Security Administrator under a plan of appointment which would assure the proper and intelligent use of the funds for educational purposes.

* * * *

The question as to how the departments will use the funds to improve pediatric teaching is pertinent. It is obvious from the statement of the committee that they have no thought of a specific program or standardization being imposed under bureaucratic control. Needs vary according to local conditions and the teaching shortcomings of one department may be quite different from those of another. Each department should be trusted to use the funds to meet what it considers its most important needs, and we know of no one better able to

judge the needs than the heads of the departments who have the responsibility for pediatric instruction in their own school. Funds might be needed by one school to increase the number of full-time teachers, and by another for salaries for part-time teachers which would enable them to give more time to teaching. The head of one department told us he would first use the funds to enlarge his staff so that he could carry instruction to a group of satellite hospitals in surrounding communities. Another stated his first use would be to develop instruction in child psychiatry, which is nonexistent in his school. These are but a few examples of the many possibilities. There would, and should be, marked differences in the use of the educational funds by the different schools.

* * * *

We fail to see the logic by which aid to medical schools from state taxes is acceptable, but is tainted when it comes from federal taxes, as the strength of the nation as a whole is dependent on the health of the nation as a whole. The medical profession has accepted the principle of federal aid for facilities for medical care under the Hill-Burton Act. Some physicians, which a reasoning quite unclear to us, link federal aid for education with the bogey of "socialized medicine," while others, particularly those associated with privately controlled institutions, fear it may in some way lead to outside control of policies and to the fixing or lowering of standards. Regardless of how the cost of medical education is met, the present high standards of medical education must not be lowered. This would be a calamity.

Certainly there is nothing socialistic or tending to the socialization of medical practice in these proposals. Such emotional diatribes as that of Dr. Black, with which the pediatricians have been circularized, will further rather than hinder support of the Committee's proposals. Quite frankly, if an attempt were made to put the handling and allotment of these educational funds in the hands of the Children's Bureau, which heretofore has had administration of federal funds for child health work, we would oppose the plan and urge our Congressmen to oppose it, as we feel a wise use of these funds could be made only if the control were in the hands of experienced educators.

* * * *

Tremendous progress has taken place in pediatric instruction and teaching and in pediatric practice in the last twenty years, as those of us who were active teachers twenty-five to thirty years ago are the first to recognize and take pride. There are, however, as the survey of pediatric education points out, tremendous gaps and marked inequalities in instruction and in the distribution of personnel well trained in the medical care of children. As stated previously, it has been our belief and contention over many years that the character and quality of medical care is basically dependent on the character and quality of medical education. It is our considered judgment and feeling that these recommendations of the Committee will decidedly improve pediatric teaching, upon which in the final analysis the quality of medical care of children depends. For this reason we believe the medical profession should support the proposals.

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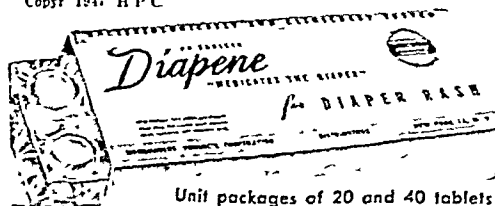
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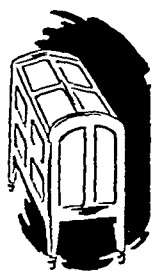
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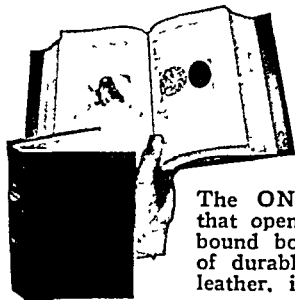
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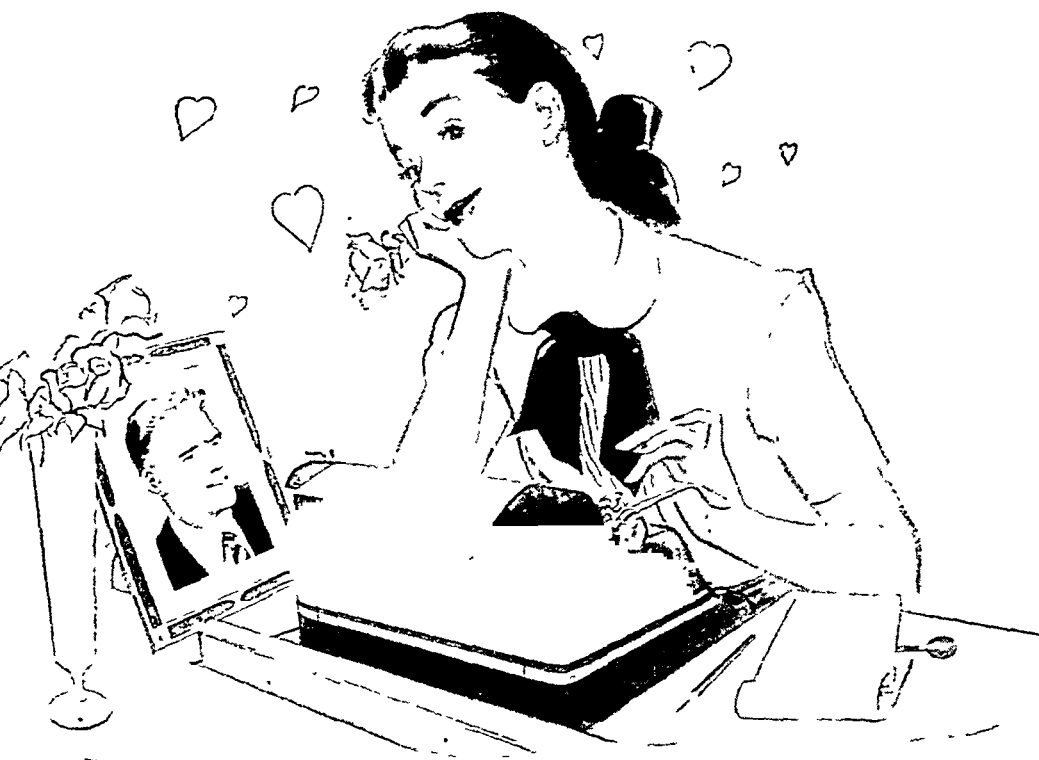
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belongs to the people. Through it, the victims of disaster receive comfort, shelter, rehabilitation aid. Through it also a new National Blood Program is being developed which eventually will provide whole blood or plasma to all who need its miraculous healing powers. Meanwhile, the Red Cross remains the constant friend of our men in uniform as well as of veterans. To the lonely, the anxious, and the sick, Red Cross stands as the sign of hope. Let's keep it at full strength by participating in the 1948 Red Cross Fund campaign.

Basil O'Connor

President

American National Red Cross



TO YOUNG WORKING GIRLS — WHETHER IN LOVE OR NOT

When a young girl goes to work, she is apt to look on her job pretty much as a fill-in between maturity and marriage.

Whether in love or not, she's confident that a handsome breadwinner will come along . . . to provide her with a nice combination of bliss and security.

"So why," she may ask, "should I save money out of what I make?"

There are a number of reasons why—all good ones. For example:

(A) The right man might not happen along

for some time.

(B) Having money of her own is a comfort to any woman, no matter how successfully she marries.

So we urge all working girls—if you're not buying U.S. Savings Bonds on a Payroll Plan, *get started now.*

It's an easy, painless, and automatic way to set aside money for the future. In ten years, you'll get back \$4 for every \$3 you put in.

Remember, girls—having money of your own may not make you *more* attractive, but it certainly won't make you *less*!

AUTOMATIC SAVING IS SURE SAVING — U.S. SAVINGS BONDS



Contributed by this magazine in co-operation with the
Magazine Publishers of America as a public service.

AMERICAN OVERSEAS AID

AND UNITED NATIONS APPEAL FOR CHILDREN

Give Them This Day . . .

The campaign of American Overseas Aid and the United Nations Appeal for Children conducted in February offers the people of the United States the privilege to demonstrate democracy through generous and voluntary gifts of money and to express intimate concern for the welfare of their fellowmen around the world today, and that they are solidly behind their government in its official program of assistance.

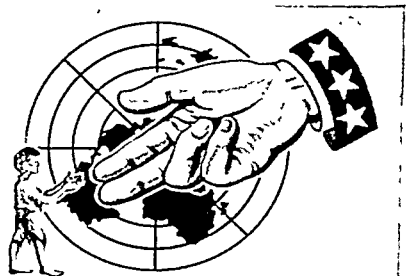
Relief of the distressed has always been a matter of American concern. In our local communities, private welfare agencies, supported by voluntary contributions, were effective in succoring needy neighbors long before the concept of public assistance became established. Similarly, a number of private American agencies, many of them representing our great religious denominations, have been carrying on works of mercy and friendship in foreign lands for generations.

The hospital in China which grew under the tender care of an American missionary . . . the nursery in France established during the terrifying days of World War I . . . the orphanage in Greece built as a direct result of American gifts . . . the religious organization-supported dental clinic in the Philippines . . . these are monuments to friendship which agencies united under the AOA-UNAC banner have built in the years gone by.

Today's needs are as critical as yesterday's; today's problems are infinitely greater. By supporting this urgent campaign, the people of the United States can give the world further proof that our democracy is keenly alert to the welfare of the world's people, proof that it is both productive and strong enough to translate concern into concrete and effective assistance.

Supplementing, as it does, governmental aid, and providing a personal link between each American and his fellowman overseas, AOA-UNAC is an indispensable stone in the arch of peace and understanding which we are resolved shall be fashioned. It is, as President Truman recently said at the White House, "essential to the program which is now in the making for the welfare of the whole world."

Give Them This Day . . . Contribute
to your local American Overseas Aid—
United Nations Appeal for Children; or
to AOA-UNAC National Headquarters,
39 Broadway, New York 6, N. Y.

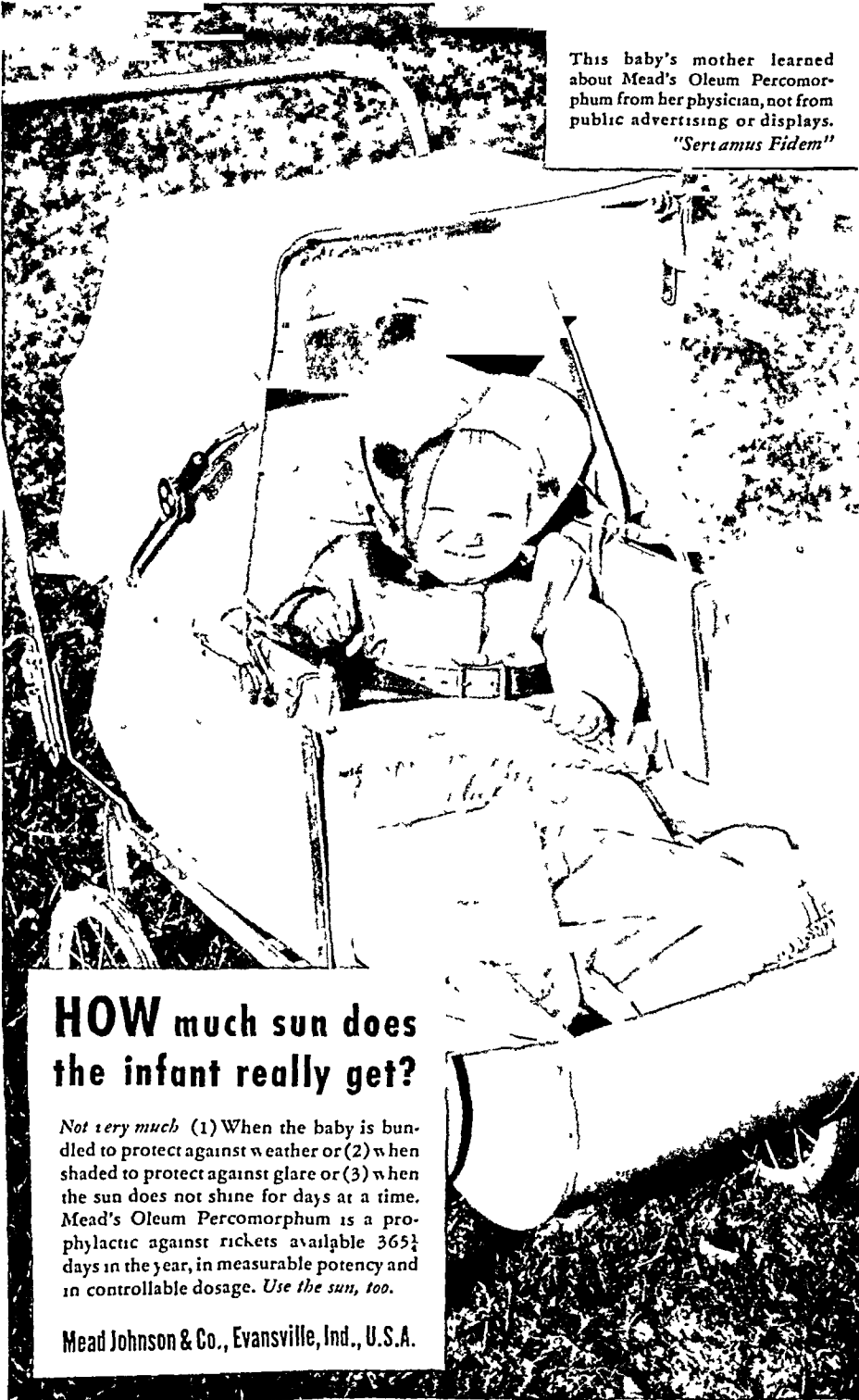


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While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



This baby's mother learned about Mead's Oleum Percomorphum from her physician, not from public advertising or displays.
"Sertamus Fidem!"

HOW much sun does the infant really get?

Not very much (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time. Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage. *Use the sun, too.*

Mead Johnson & Co., Evansville, Ind., U.S.A.

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"protein

CHILD HEALTH CENTER
UNIVERSITY OF WASHINGTON

D

efficiency [in children]

is much more common

than is generally realized."*



Investigators have shown that when the variety of foods is limited — as in infant feeding — care must be exercised in their selection . . . the chief consideration being "the furnishing of the essential amino acids to be made available to the tissues by digestion."*

DRYCO, spray-dried for ready reconstitution in cold or warm water, provides the physician with a remarkably flexible basic high protein food, containing all the essential amino acids. It is ideally suited to the changing nutritional requirements of the normal or abnormal infant. Easily digestible (because of its soft curd characteristics), bacteriologically safe and constant in composition — this vitamin-fortified, improved, infant food may be readily adapted to six distinct types of formulas:

- 1 DRYCO alone (*high protein, low fat, low carbohydrate*).
- 2 DRYCO with carbohydrate (*high protein, low fat, high carbohydrate*).
- 3 DRYCO with whole milk — fresh, evaporated or dried (*high protein, intermediate fat, low carbohydrate*).
- 4 DRYCO with whole milk — fresh, evaporated or dried — and carbohydrate (*high protein, intermediate fat, high carbohydrate*).
- 5 DRYCO with skim milk — fresh or dried (*high protein, exceptionally low fat, low carbohydrate*).
- 6 DRYCO with skim milk — fresh or dried — and carbohydrate (*high protein, exceptionally low fat, high carbohydrate*).

*A.M.A.: *Handbook of Nutrition*, Chicago, 1943.

BORDEN'S PRESCRIPTION PRODUCTS DIVISION
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DRYCO is made from spray-dried, pasteurized, superior quality whole milk and skim milk, providing 2500 U.S.P. units of vitamin A and 400 U.S.P. units of vitamin D per reconstituted quart. Each tablespoon supplies 31½ calories. Dryco is available at all pharmacies in 1 and 2½ lb. cans.



DRYCO

the "Custom Formula" high protein infant food



Vol. 32

APRIL, 1948

No. 4

307M
d/s
K.C.

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

Editor

BORDEN S. VEEDER
St. Louis

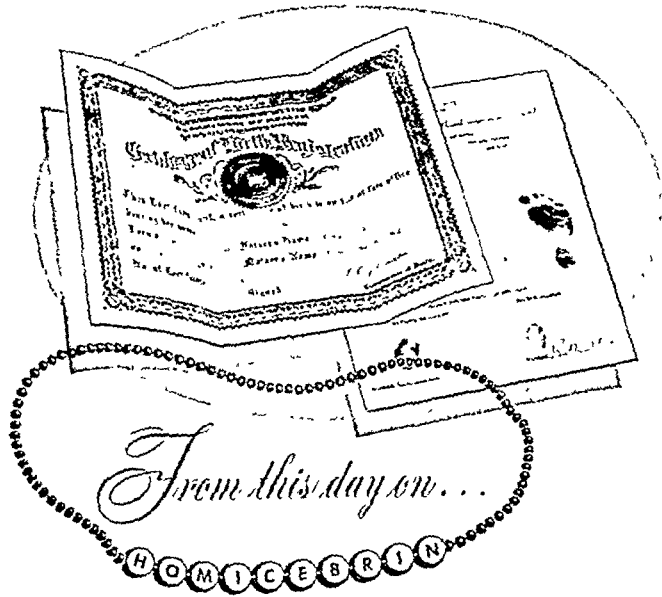
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(Homogenized Vitamins A, B₁, B₂, C, and D, Lilly)


THE DIET OF AN INFANT soon after birth becomes the prime problem in getting the child off to a good start. Variations in the diet must often be based on tolerance, with little attention to vitamin values. Early avitaminosis may develop during periods of dietary adjustment.

One average teaspoonful (5 cc.) of 'Homicebrin' (Homogenized Vitamins A, B₁, B₂, C, and D, Lilly) contains up to two times the daily allowance of the essential vitamins A, B₁, B₂, C, and D.

This homogenized preparation is pleasantly flavored and is completely free from a fish-oil taste or odor.

'Homicebrin' is available in bottles of 60 cc. and 120 cc. at retail drug stores everywhere.

ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA. U. S. A



This baby's mother learned
about Mead's Oleum Percomor-
phum from her physician, not from
public advertising or displays.

"Sertamus Fidem"

HOW much sun does the infant really get?

Not very much. (1) When the baby is bundled to protect against weather or (2) when shaded to protect against glare or (3) when the sun does not shine for days at a time. Mead's Oleum Percomorphum is a prophylactic against rickets available 365½ days in the year, in measurable potency and in controllable dosage. *Use the sun, too.*

Mead Johnson & Co., Evansville, Ind., U.S.A.

The Basis for an Optimum Diet for Infants

Excerpts from:

GROWTH AND DEVELOPMENT OF THE YOUNG CHILD

by

Winifred Rand, A.B., R.N.; Mary E. Sweeney, A.M., M.S. and E. Lee Vincent, Ph.D.
Fourth Edition W. B. Saunders Co., Phila., London 1915

In order to grow an inch a month during the first year and to double his weight in the first 6 months, [infants] must have not only a sufficient quantity of food, but it must provide all the amino acids that are nutritively essential, and the vitamins and the minerals necessary for optimum growth and health.—Page 219

All food substances needed by the body are equally important although required in widely differing amounts... the importance of maintaining balance in the nutrient is one of the more recent contributions to our knowledge of the nutrition of human beings.—Page 223

BRENNEMANN'S PRACTICE OF PEDIATRICS

by

Various Authors—Edited by Irvine McQuarrie, A.B., Ph.D., M.D.
Hagerstown, Maryland—W. F. Prior Company, Inc. 1945
Volume I Chapter 27

All of the vitamins are necessary for normal growth and development and play an important part in resistance to infection.—Page 17

These Soups are Nutritionally Proportioned Meat-and-Vegetable Foods

Specifically: There are four of these meat-and-vegetable foods—Chicken, Beef, Lamb and Liver—each with 5 to 7 of the green and yellow vegetables, and cereal, in addition to the meat. Each provides an entire meat-and-vegetable main dish for a baby's meal.

There is a fifth food—All-Vegetable—consisting of eight vegetables, plus oatmeal. This, complemented with egg yolk, makes for a nutritionally proportioned meal.

All of these foods are of smooth, strained consistency; may be fed to even extremely young babies.

Together these five strained foods help insure any baby a balanced wholesome diet.

They come packed in glass jars—ready-cooked, ready to use. Require nothing but heating.

Campbell's

**STRAINED MEAT-AND-VEGETABLE
BABY SOUPS**



LOOK FOR THE
RED-AND-WHITE LABEL

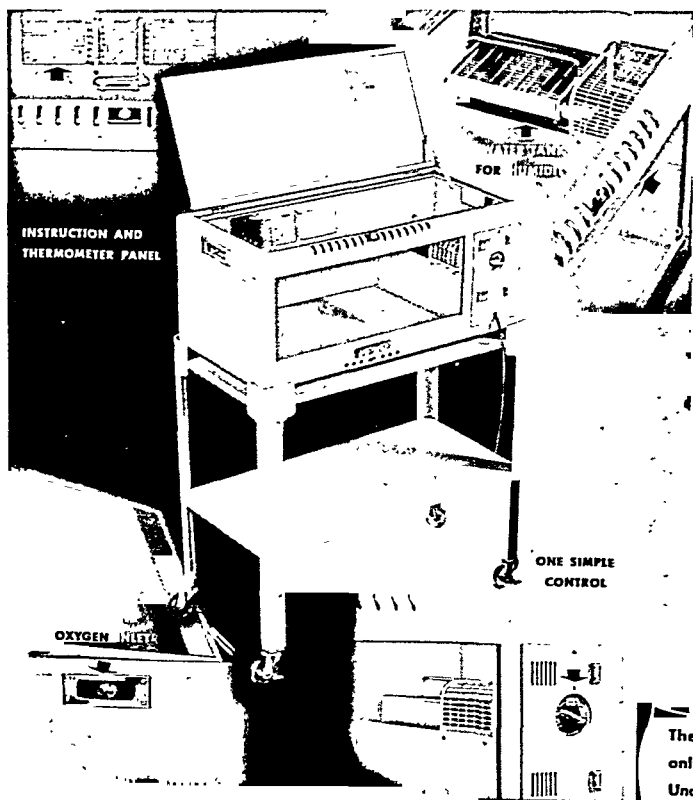
The baby foods that contain—

Chicken	+ 5 Vegetables + Semolina
Beef	+ 6 Vegetables + Egg Noodles
Lamb	+ 5 Vegetables + Barley
Liver	+ 7 Vegetables + Oatmeal
Vegetable	= 8 Vegetables + Oatmeal

*Dietetic analyses of these strained foods
will be sent to any doctor upon request.*

Every grocer who sells Campbell's Soups can supply Campbell's meat-and-vegetable Baby Soups

ARMSTRONG X-4 PORTABLE BABY INCUBATOR



1. Low cost
2. Underwriter approved
3. Simple to operate
4. Only 1 control dial
5. Safe, low-cost, heat
6. Easy to clean
7. Quiet and easy to move
8. Ball-bearing, soft rubber casters
9. Fireproof construction
10. Excellent oxygen tent
11. Welded steel construction
12. 3-ply safety glass
13. Full length view of baby
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15. Night light over control
16. Both F. and C. thermometer scales
17. Safe locking ventilator
18. Low operating cost
19. Automatic control
20. No special service parts
21. Lid locks open

The Armstrong X-4 Baby Incubator is the only Baby Incubator tested and approved by Underwriters' Laboratories for use with oxygen.

● In offering you the Armstrong X-4 Portable Baby Incubator we stand firmly on the principle that we must provide a **SAFE** Baby Incubator, a **LOW COST** Baby Incubator and a **SIMPLE** Baby Incubator.

That we have succeeded is evidenced by the fact that to date close to 400 Hospitals have placed voluntary repeat orders for more than 1200 additional Incubators. More and more it is being used, not only for the premature baby, but for any debilitated or under weight baby.

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Children love to eat sweets . . . a desire easily turned to therapeutic advantage when medicines are prescribed in *Dulcet* Tablet form. *Dulcet* Tablets resemble delicious candies so much in appearance and taste that children readily accept each dose as a candy treat—even when the *Dulcet* Tablets contain such potent agents as the sulfonamide compounds. *Dulcet* Tablets are as accurately medicated and standardized as other tablet forms, and will produce the same therapeutic results when used at the same level of dosage. All of the commonly used sulfonamide compounds—plus the new mixture of sulfadiazine and sulfathiazole, Diazoline—are available in *Dulcet* Tablet form, each agent in a different color and flavor. On your next prescription for sulfonamides, be sure to specify *Dulcet* Tablets. ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS.

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Sulfamerazine *Dulcet* Tablets, 0.3 Gm.

Diazoline* *Dulcet* Tablets, 0.3 Gm.

[Compound Sulfadiazine, 0.15 Gm. and Sulfathiazole, 0.15 Gm., Abbott]

*TRADE MARK

Specify

DULCET

Tablets

(MEDICATED SUGAR TABLETS, ABBOTT)

started in
hospital
and
continued
at home*



*"Every infant, including every breast-fed infant, should receive vitamin D by mouth as early as practicable."**

White's Cod Liver Oil Concentrate Liquid provides natural vitamins A and D of time-proved cod liver oil—at a cost-to-patient of about a penny a day for antirachitic protection for the average infant. In Liquid form for drop dosage to infants—convenient, palatable, economical. Also available in Tablets and Capsules.

*Clements, F. W.: Rickets in Infants under One Year. The Incidence in an Australian Community and a Consideration of the Etiological Factors. Med. J. Australia, 1:336 (1942).

White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.



"Older children require prophylactic doses of vitamin D until maturity, especially during periods of rapid growth."²

White's Cod Liver Oil Concentrate Tablets provide a pleasant, economical means of supplying *assured* antirachitic protection—wholly natural vitamins A and D in a form older children (2-14 years of age) enjoy taking regularly.

White's Cod Liver Oil Concentrate is wholly derived from time-proven cod liver oil itself. Liquid, Tablet and Capsule forms

**A FOOD UNLIKE ANY
OTHER INFANT FOOD
DESPITE THE CONFUSING
SIMILARITY OF NAMES**



THE FAT of Similac is not all butter fat, but a homogenized combination of fats that is balanced chemically and metabolically to the infant's requirements.

THE PROTEIN of Similac is rendered soluble to a point approximating the soluble protein in human milk.

THE CARBOHYDRATE in Similac is lactose.

THE MINERALS in Similac are adjusted to closely approximate the minerals of breast milk.

THE CURD TENSION of Similac is the same as that of breast milk—consistently zero.

No other substitute resembles breast milk in all of these essential respects.

M & R DIETETIC LABORATORIES, INC. • COLUMBUS 16, OHIO



A powdered, modified milk product, especially prepared for infant feeding, made from tuberculin tested cow's milk (casein modified) from which part of the butter fat has been removed and to which has been added lactose, coconut oil, cocoa butter, corn oil, and olive oil. Each quart of normal dilution Similac contains approximately 400 U.S.P. units of Vitamin D and 2500 U.S.P. units of Vitamin A as a result of the addition of fish liver oil concentrate.

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*Similar to
breast milk*



when you want...

**a minimum
of drowsiness**

**a minimum of
other side reactions**

**a high degree of
effectiveness**

**...in the antihistamine
treatment of
allergic disorders**

THEPHORIN

Brand
of
Phenindamine

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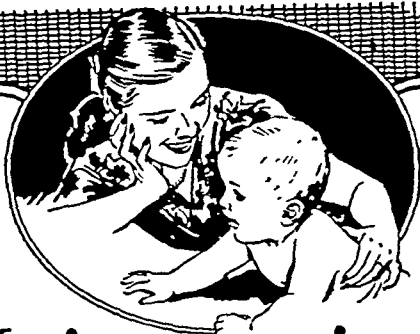
Available in 25 mg tablets
and syrup containing 10 mg per 4 cc.

H O F F M A N N - L A R O C H E I N C .

NUTLEY 10 • NEW JERSEY

T. M. — THEPHORIN — REG. U. S. PAT. OFF.

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Beech-Nut is running in newspapers
and magazines to reach mothers



Have your doctor back
up the judgment of
YOUR baby.

It is amazing
what a mother can learn from a
3 months old baby—*but doctors know*

The specialist in infant feeding says, "Don't force your child to eat too much; baby will let you know when he wants to eat, and when he has had enough."

That is important—but equally as important is the food you select for your baby.

Since the beginning Beech-Nut has cooperated with doctors in the selection and processing of these foods. They are all scientifically prepared in spotless kitchens—the food flavors and values are retained in high degree—babies like them and thrive on them.

Beech-Nut

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"ACCEPTED"



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For Children

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This preparation readily implants a strain of *Lactobacillus acidophilus* . . . providing an aciduric intestinal flora . . . favoring normal colonic function. Neo-Cultol is a suspension of viable *Lactobacillus acidophilus* in a chocolate-flavored mineral oil jelly whose composition is adjusted to give mild lubrication without leakage. Its chocolate flavor readily appeals to children.

To correct intestinal stasis in children, prescribe

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REG. U. S. PAT. OFF.

Lactobacillus Acidophilus in a Refined Mineral Oil Jelly Chocolate Flavored

Dosage: One to 2 teaspoonfuls at night on retiring.

Supplied: In jars containing 6 ounces.

THE ARLINGTON CHEMICAL CO.

Arlington

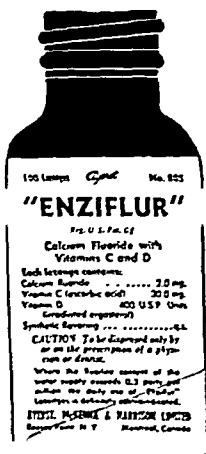
YONKERS 1

NEW YORK

*The word "NEO-CULTOL" is a registered trademark of The Arlington Chemical Company.



as an aid in the prevention of...
dental caries



Fluorine therapy in easily controllable form is offered by "Enziflur" Lozenges, each of which provides 2.0 mg. calcium fluoride,* 30.0 mg. Vitamin C (ascorbic acid) and 400 U. S. P. Units Vitamin D (irradiated ergosterol).

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Descriptive literature outlining indications, dosages and contraindications available to dentists upon request.

*approximately 1 mg. fluorine

"Enziflur" Lozenges (No. 805) are supplied in bottles of 30, 100 and 1000.

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 New York 16, New York



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aggravates, or prolongs

**DIAPER RASH and
INFANTILE ECZEMAS**

LOWILA

CAKE for skin cleansing

The only detergent cake which is entirely soapless yet cleanses as well as soap. No alkali whatsoever, pH approximates normal skin, never irritates. Less slippery than ordinary soap so mother can hold baby more firmly while bathing. Good lather.

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lathering
detergents

LIQUID for clothes and household

Washes diapers, bed clothes, infant wear beautifully; soapless and non-irritant in proper dilution. Does not leave the alkaline, irritating residue left by soaps.



For **SAMPLES** and literature **SEND COUPON**

WESTWOOD Pharmacal Corp.

468 Dewitt St., Buffalo 13, N. Y., Dept. J.P.

Convince me with **TRIAL SUPPLY** and literature
LoWILA cake and liquid

Dr.....

Address.....

IN 48 HOURS

Sulfonamides in an alkaline liquid suspension have a definite role in modern chemotherapy by reason of (1) lowered renal toxicity, (2) quicker and higher blood levels. With such potent drugs in liquid form, the matter of positive, uniform dosage teaspoon after teaspoon is of first importance.

The Original Liquid Sulfonamides

Donley-Evans have conducted continuous research toward improved stability of product. As the alkalinizing vehicle for liquid sulfonamides, an especially purified sodium lactate (developed by Donley-Evans) not only assures optimum renal protection but also stability, safety and palatability of the highest order.

GLUCO-Sulfonamides

(DONLEY-EVANS)


The GLUCO-SULFONAMIDES, as the finest liquid preparations available, form an important part of the modern armamentarium, especially in treating infectious diseases in children or in the aged where renal insufficiency may exist.

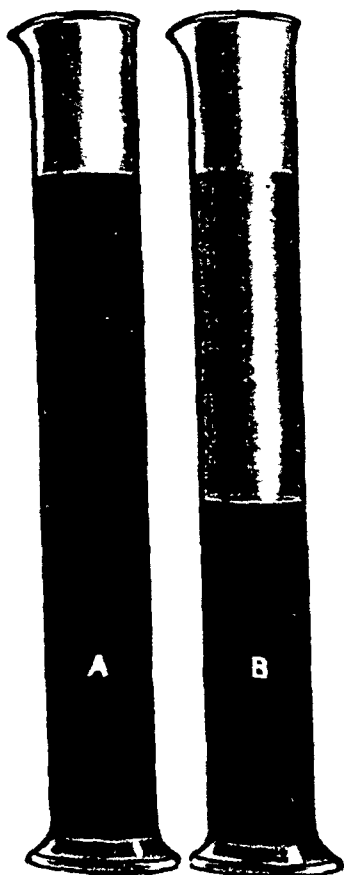
For complete uniformity and stability of product, you may rely on the Donley-Evans' pharmaceutical skill in the accurate dosage, on which therapeutic effectiveness and safety depend. The GLUCO-SULFONAMIDES contain—approximately 1 Gram of sodium lactate to the teaspoon, or 21.6 Grams per 100 cc.

Supplied: At prescription pharmacies in 6 oz. and pint bottles. Each 5 cc. (one teaspoonful) contains 5 grains of sulfonamide in a sodium lactate-glucose base.

GLUCO-SULFADIAZINE GLUCO-SULFATHIAZOLE
GLUCO-SULFAMERAZINE GLUCO-SULFANILAMIDE

DONLEY-EVANS & COMPANY

ST. LOUIS 15  MISSOURI



A. GLUCO-SULFADIAZINE on standing shows uniform suspension without separation.

B. A liquid sulfadiazine made with the usual suspending agents shows, even in 48 hours, separation and precipitation which might impede accurate dosage.



IMPETIGO responds *quickly* to

Hitherto difficult to control, impetigo has shown dramatic response to Sulfa-Ceepryn Cream—clinical reports indicating that a majority of cases are cleared *within three days*.

Sulfa-Ceepryn Cream provides a rational "three-way" combination of 10% sulfathiazole (antistaphylococcic), 10% sulfanilamide (antistreptococcic), and Ceepryn 1:500 (germicidal detergent).

Ceepryn, having a wetting action that permits quick penetration into the lesion and a bactericidal action that is particularly effective against pyogenic cocci, reinforces the action and widens the range of the sulfonamides. The special water-miscible, vanishing cream base facilitates easy spreading and

Sulfa-Ceepryn

Sulfathiazole, Sulfanilamide and Cetylpyridinium Chloride

Cream

rapid absorption of the active ingredients.

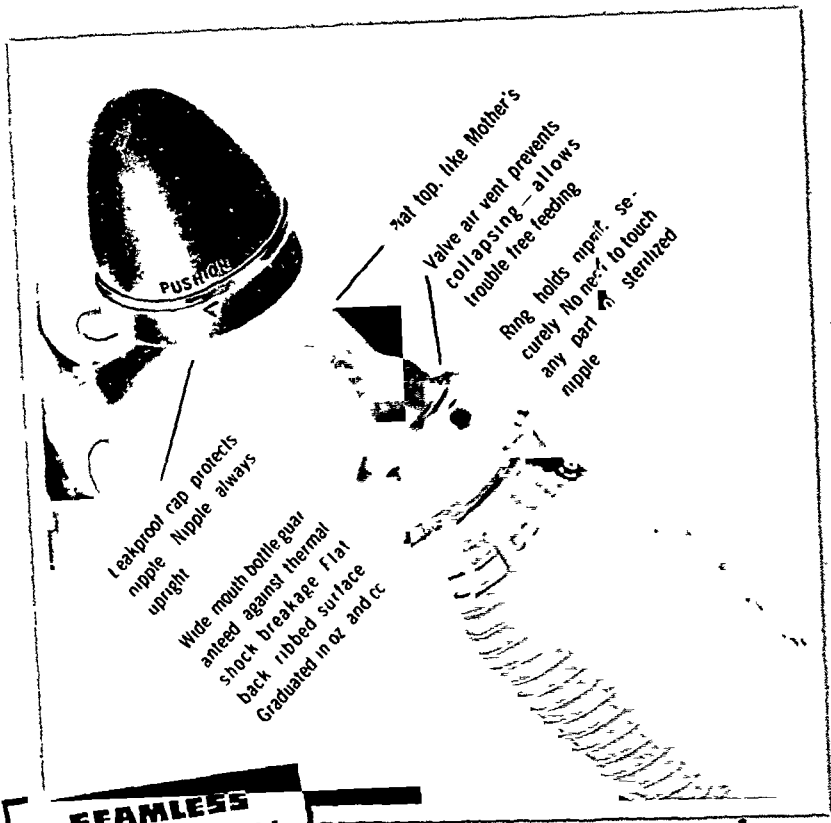
Sulfa-Ceepryn Cream is equally effective in other dermatological pyogenic infections, also adjunctively in varicose, wound, and abscess infections, following surgical drainage. Bandaging is not contraindicated. Complete literature and sample on request.

Sulfa-Ceepryn Cream is available at prescription pharmacies in 1-ounce tubes and 1-pound jars

Trademarks Sulfa-Ceepryn and Ceepryn Reg U S Pat Off



THE WM. S. MERRELL COMPANY • CINCINNATI, U. S. A.



**SEAMLESS
EVEREADY
NURSER**

"Lift the Cap—Feed the Baby!"

SAFER . . . EASIER . . . 6 FEATURES!

Little or no "air-colic"—little or no spitting up! Easier to use—no need to reverse nipple—no fumbling. Just warm the bottle, "Lift the Cap—Feed the Baby!" . . . Recommend the EVEREADY Nurer. Mothers will thank you!

FINEST QUALITY SINCE 1877



REG
U S
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OFF

**RUBBER SUNDRIES DIVISION
THE SEAMLESS RUBBER COMPANY
NEW HAVEN 3, CONN., U. S. A.**

"Out of the mouth of babes....."



Vomiting of infancy when caused by pylorospasm, as well as intestinal colic due to spasm, is often relieved by the administration of atropine. However, atropine commonly produces undesirable side effects on widely separated and unrelated parts of the body. In contrast, Mesopin permits more selective management of gastrointestinal spasticity without the untoward effects of atropine and similar antispasmodics. When spastic pain is due to nervous irritability or improper digestion, sedative medication and dietary regulation are also indicated.

The average dose of Mesopin for infants is 0.6 mg. (1/100 gr.) given shortly before each feeding. One-quarter of a tablet of Mesopin may be crushed and mixed with water or other liquids.

Mesopin is supplied in tablets of 2.5 mg. (1/24 gr.).

Samples sent on request.



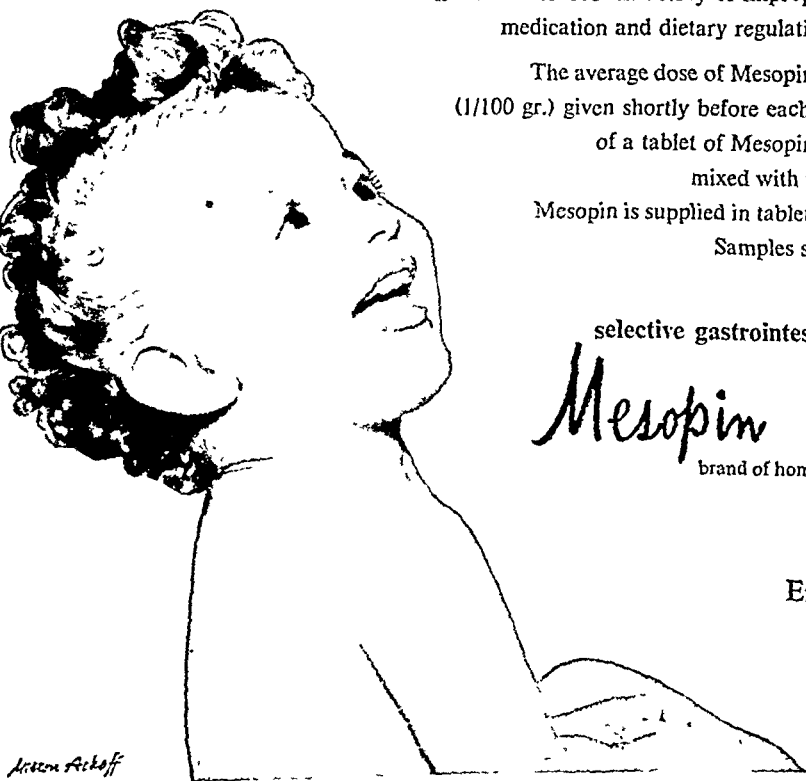
selective gastrointestinal antispasmodic

Mesopin

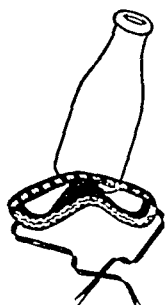
brand of homatropine methyl bromide

Endo Products Inc.

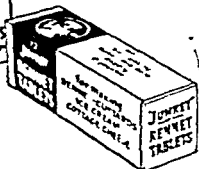
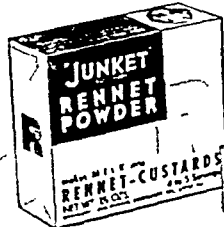
Richmond Hill 18, N. Y.



"make milk a blessing in disguise!"



"JUNKET" is the trade-mark of Chr. Hansen's Laboratory, Inc., for its rennet and other food products, and is registered in the United States and Canada



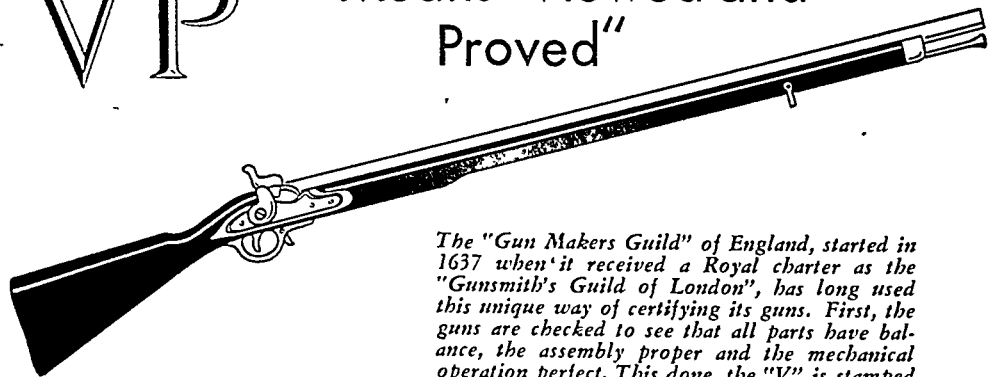
When milk is an essential nutritional factor (as in infancy, early childhood, pregnancy, gastro-intestinal and post-operative conditions), and yet it cannot—or will not—be taken by the patient... try "dressing up" this dietary "must", with the aid of "Junket" Brand Rennet Powder or Tablets. They make uncooked milk a true blessing in disguise by transforming it (easily and quickly) into appealing, flavorful rennet desserts. Rennet desserts are not only tempting to eye and palate; they retain the nutritional values of milk, yet are more easily and rapidly digested by virtue of the softer, finer, more flocculent curds produced in the stomach by rennin's enzymatic action. "Junket" Rennet Powder is available in six natural flavors, already sweetened; "Junket" Rennet Tablets are supplied unsweetened and unflavored (particularly valuable for diabetics).

"JUNKET" BRAND FOODS

Division of Chr. Hansen's Laboratory, Inc.
LITTLE FALLS, N. Y.

VP

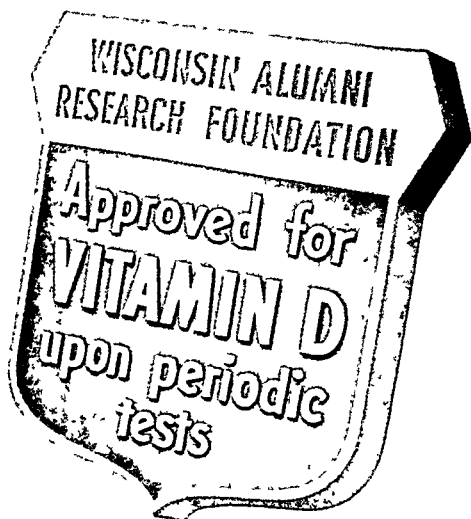
Means "Viewed and Proved"



The "Gun Makers Guild" of England, started in 1637 when it received a Royal charter as the "Gunsmith's Guild of London", has long used this unique way of certifying its guns. First, the guns are checked to see that all parts have balance, the assembly proper and the mechanical operation perfect. This done, the "V" is stamped to mean "Viewed". Next the gun is fired with heavy charges. After this "Proving", the "P" is stamped. And there's your warranty.

... and this seal has a similar meaning

For the Wisconsin Alumni Research Foundation seal or mention of the Foundation name attests to the Vitamin D content of a product. This seal guarantees that these products are tested in the Foundation's laboratories at regular intervals to make certain they measure up to its high standards and rigid requirements. For almost 2 decades the medical profession has advised its patients, "Look for the Foundation seal." It's assurance of standard quality.



WISCONSIN ALUMNI *Research* FOUNDATION
MADISON 6, WISCONSIN



BABY'S FIRST BIRTHDAY

One little candle gleaming bright—yet not half as bright as the tender, contented light in mother's eyes!

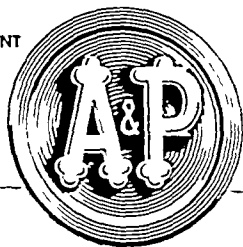
Her youngster is the picture of health, and mother is justly proud of her wisdom in selecting White House Milk for the formula. Doctors approve White House, for they know it's nourishing and generously provides pure vitamin D₃. There's none better!

WHITE HOUSE MILK

There's None Better

400 U.S. UNITS OF PURE VITAMIN D₃ PER PINT

*Mother's first thought
for infant feeding!*



Satisfaction Guaranteed or money back by A&P

*Not Connected With Any Other Company Using A Similar Name or Brand.

FASTER MORE PROLONGED ACTION

... without over sedation **T-BARDRIN** (Angier) Rectal Suppositories

A stable combination of ephedrine and theophylline, with adequate sedation, highly effective in a greater percentage of BOTH ASTHMA AND HAY FEVER CASES . . . especially in patients who are "epinephrine-fast".

FORMULA:

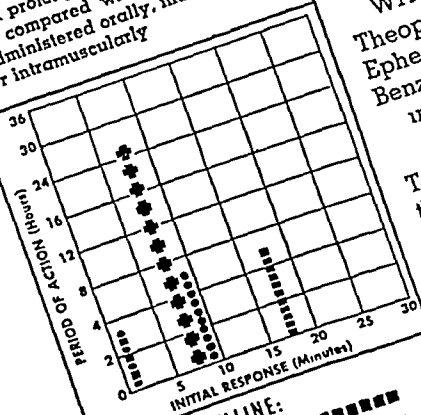
Each T-Bardrin suppository contains:
 Pentobarbital sodium 0.05 gm.
 Phenobarbital sodium 0.05 gm.
 Theophylline 0.40 gm.
 Ephedrine hydrochloride 0.05 gm.
 Benzocaine 0.06 gm.
 in a cocoa butter base

T-Bardrin (Angier) may be employed therapeutically or prophylactically. Administration may be made at the onset of an acute attack, or routinely should the patient experience the NORMAL 24 TO 36 HOUR PERIOD OF RELIEF.

Samples and further information furnished when requested on professional letterhead

ANGIER CHEMICAL COMPANY
 Boston 34, Massachusetts

Chart illustrating initial response and prolonged action of T-BARDRIN as compared with aminophylline administered orally, intravenously or intramuscularly



AMINOPHYLLINE:

Oral
 Intravenous
 Intramuscular
 T-BARDRIN

PIONEERS in Research...and Leadership thru the years in combating OTITIS MEDIA



DOHO in realizing the need for a potent, topical, well tolerated ear medication, yet mindful that no one formula could be suitable for all conditions...devoted every facility and scientific resource to the development and perfection of AURALGAN and OTOSMO-SAN. Each has its sphere of usefulness... each has been tested and clinically proven in many thousands of cases. *Reprints and substantiating data sent on request.*

EACH A SPECIFIC...both effective!

Auralgan
IN ACUTE OTITIS MEDIA

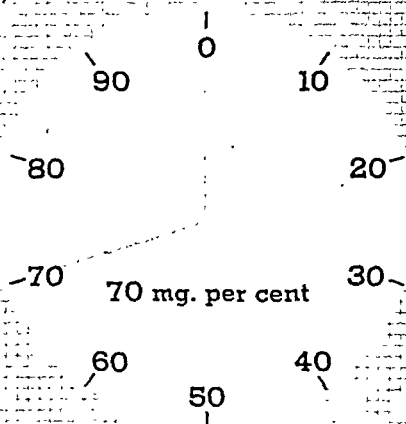
is a scientifically prepared, completely water-free Glycerol (DOHO) having the highest specific gravity obtainable, containing antipyrine and benzocaine... which by its potent decongestant, dehydrating and analgesic action provides effective relief of pain and inflammation.

O-TOS-MO-SAN
IN CHRONIC SUPPURATIVE
OTITIS MEDIA, FURUNCULOSIS
AND AURAL DERMATITIS

is not just a mere mixture, but a scientifically potent chemical combination of Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) base... which exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

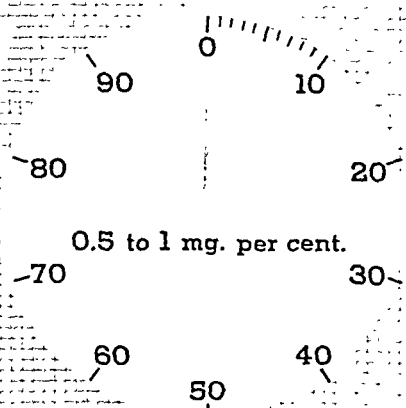
Literature and samples on request

THE DOHO CHEMICAL CORPORATION
New York 13, N. Y. • Montreal • London



HIGH Local Sulfonamide Concentration

A single tablet of White's Sulfathiazole Gum chewed for one hour, *maintains* a high, effective *salivary* concentration of *locally* active sulfathiazole averaging 70 mg. per cent.



Negligible Systemic Absorption

With maximal dosage of Sulfathiazole Gum, even in children, blood levels of sulfonamide are usually too low to be quantitatively measurable, rarely approaching 0.5 to 1 mg. per cent. The gum vehicle serves as a "reservoir" for the drug which is released slowly at a rate roughly paralleling the drug's solubility in saliva. Systemic absorption is so limited that toxic reactions are virtually ruled out.

The clinical value and safety of White's Sulfathiazole Gum in the topical treatment of oropharyngeal infections has been established by longer professional use than any other local chemotherapeutic or antibiotic agent. Full stability and, therefore, potency is retained under all ordinary conditions.

Supplied in packages of 24 tablets— $3\frac{3}{4}$ grs. (0.25 Gm.) per tablet—sanitaped, in slip-sleeve prescription boxes.

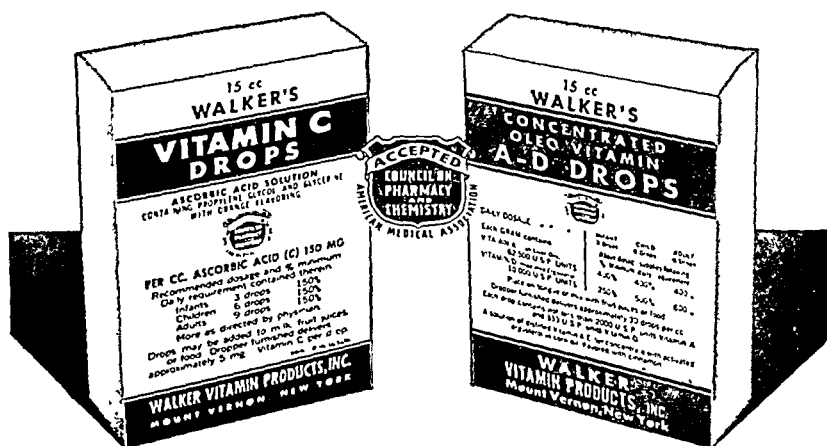
LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

sulfathiazole gum

SAFE, TOPICAL CHEMOTHERAPY

WALKER

COUNCIL-ACCEPTED VITAMIN DROPS



Potent, convenient, flexible dosage form
Designated for use in pediatrics and geriatrics

VITAMIN C DROPS

Each drop supplies 5 mg. of vitamin C

Supplied in dropper bottles of 15 cc.

CONCENTRATED OLEO VITAMIN A-D DROPS

Each drop supplies 2,000 units vitamin A, 333 units vitamin D

Supplied in dropper bottles of 15 cc. and 60 cc.

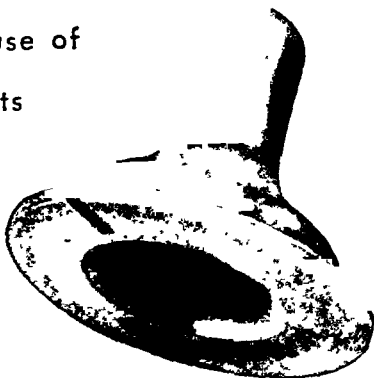
Walker

VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.

The answer to increasing use of
oil-base vitamin supplements

THE NEW

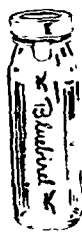
Bluebird
NURSER



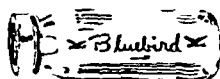
with the **first** and **only OILPROOF NIPPLE**
(one set should see baby through infancy!)



Ready for
Feeding



Ready for
Storage



Leakproof in Any Position
May Be Stored On Side

THE NEW BLUEBIRD NIPPLE*
offers all these important advantages:

- completely resistant to all oils
- feeding orifices remain uniform
- will not soften, swell or stretch or collapse through months of use and sterilization
- texture is firm, flesh-like, designed to stimulate sucking
- resistant to temperatures that will destroy rubber nipples
- non-reversible nipple valve permits regulation of milk flow

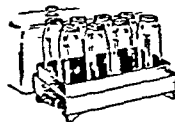
* made of Flecton—a new, tough, oil-resistant, dense material of low porosity, with tensile strength and tear-resistance many times that of natural rubber.



Bluebird sealer disc
of wafer-thin metal is un-
breakable, completely
heat-resistant.



Bluebird retainer cap
holds nipple firmly in place.
Slight twist regulates milk
flow as desired.



Bluebird bottle is Slo-Annealed
Glass for lowest possible break-
age and freedom from toxic ma-
terials sometimes found in glass.



Bluebird NURSER • COSHOCTON, OHIO

For surface infections...



New and Nonofficial Remedies • 1947 • states: "NITROFURAZONE.—Furacin... possessing bacteriostatic and bactericidal properties . . . effective in vitro and in vivo against a variety of gram negative and gram positive bacteria . . . is useful for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulceration and certain diseases of the skin . . . Variant bacterial strains showing induced resistance to sulfathiazole, penicillin or streptomycin are as susceptible to nitrofurazone as their parent strains . . ." Furacin N.N.R. is available in the form of Furacin Soluble Dressing containing 0.2 per cent Furacin. This preparation is indicated for topical application in the prophylaxis and treatment of infections of wounds, second and third degree burns, cutaneous ulcers, pyoderms and skin grafts. Literature on request. EATON LABORATORIES, INC., NORWICH, N. Y., — TORONTO, CANADA

In Secondary Anemia

Not Only Iron...but also B Complex Vitamins and Liver

Not infrequently hypochromic anemia is complicated by associated nutritional deficiencies. Anorexia, disturbed gastrointestinal function, listlessness and easy fatigability are often observed concurrent with secondary anemia; in many if not all such instances deficiencies of one or more of the B complex vitamins may be responsible.



LIVITAMIN-WITH-IRON provides rapidly effective iron in readily utilizable, nonionic, minimally irritating form. In addition it supplies significant amounts of synthetic thiamine, riboflavin, nicotinamide, pyridoxine and pantothenic acid, as well as these and other vitamin B complex factors found in rice bran extract and in liver concentrate.

LIVITAMIN-WITH-IRON is indicated in hypochromic (secondary) anemia, particularly when accompanied by evidence of B complex deficiency states. It is highly efficacious whether the anemia is due to acute or chronic blood loss, deficient iron intake, infectious and other toxic states, pregnancy, or lactation.

The palatability of LIVITAMIN-WITH-IRON makes it readily acceptable to children as well as adults.

DOSAGE: 3 to 4 teaspoonfuls three times daily.



LIVITAMIN WITH IRON

Each fluidounce of Livitamin With Iron, prepared with an attractive, palatable vehicle, presents:

Iron and Manganese Peptonized.....	30 gr.
(Equivalent to 45 mg. elementary Iron)	
Iron Peptonized, N.F.....	12½ gr.
(Equivalent to 140 mg. elementary Iron)	
Thiamine Hydrochloride (B ₁).....	10 mg.
Riboflavin (B ₂ , G).....	5 mg.
Nicotinamide (Niacinamide).....	25 mg.
Pyridoxine Hydrochloride (B ₆).....	1 mg.
Pantothenic Acid.....	5 mg.
Liver Concentrate 1:20.....	45 gr.
(Represents 2 oz. fresh liver)	
Rice Bran Extract.....	15 gr.

THE S. E. MASSENGILL COMPANY

Bristol, Tenn.-Va.

NEW YORK • SAN FRANCISCO • KANSAS CITY



When these PARASITES STRIKE *KWELL* OINTMENT IS SPECIFICALLY INDICATED

Scabies and pediculosis are rapidly brought under control by Kwell Ointment. One application usually suffices in the majority of patients, regardless of the extent of the invasion. No single instance of dermatitis or skin irritation due to the active ingredient has been reported. Kwell Ointment contains the gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane (1%) in a vanishing cream base. May be safely used on tender skin areas and on infants' skin. Available on prescription at all pharmacies in 2 oz. and 1 lb. jars.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION
17 E. 43rd ST. NEW YORK 17, N. Y.

Rapidly effective on
SCABIES...ALL FORMS OF PEDICULOSIS



Formulac

**a flexible
formula basis**



FORMULAC Infant Food is a product of National Dairy research — a concentrated milk containing all the vitamins and minerals a normal infant is known to need. The vitamins are in the milk itself, reducing the risk of error or oversight in supplementary administration.

The only carbohydrate in **FORMULAC** is the normal lactose found in cow's milk. This permits you to prescribe both the type and amount of carbohydrate each individual child requires.

FORMULAC is in convenient liquid form, for easy preparation. The addition of water and sugar, at your discretion, creates a complete infant diet for normal and difficult feeding cases.

FORMULAC is promoted ethically. It has been clinically tested and proved, and retains its vitamin potency on storage. Economically priced, this product of National Dairy research is available at drug and grocery stores everywhere.

DISTRIBUTED BY KRAFT FOODS COMPANY

NATIONAL DAIRY PRODUCTS COMPANY, INC.
NEW YORK, N. Y.

For further information about **FORMULAC**, drop a card to National Dairy Products Co., Inc., 230 Park Avenue, New York 17, N. Y.



A new, improved SEAL



Crystalline Penicillin G Sodium Merck is now supplied in vials with a new, improved aluminum seal.

Among the advantages provided by this new seal are:

- The round tear-off tab is easily removable and eliminates the necessity of using a knife or other implement to pry up the tab.
- The tight-fitting dust cap with skirt provides protection for the rubber stopper during storage of the vial between injections.

Crystalline Penicillin G Sodium Merck is a highly purified product from which therapeutically inert materials have been virtually eliminated.

For Penicillin of the highest quality—

SPECIFY MERCK!

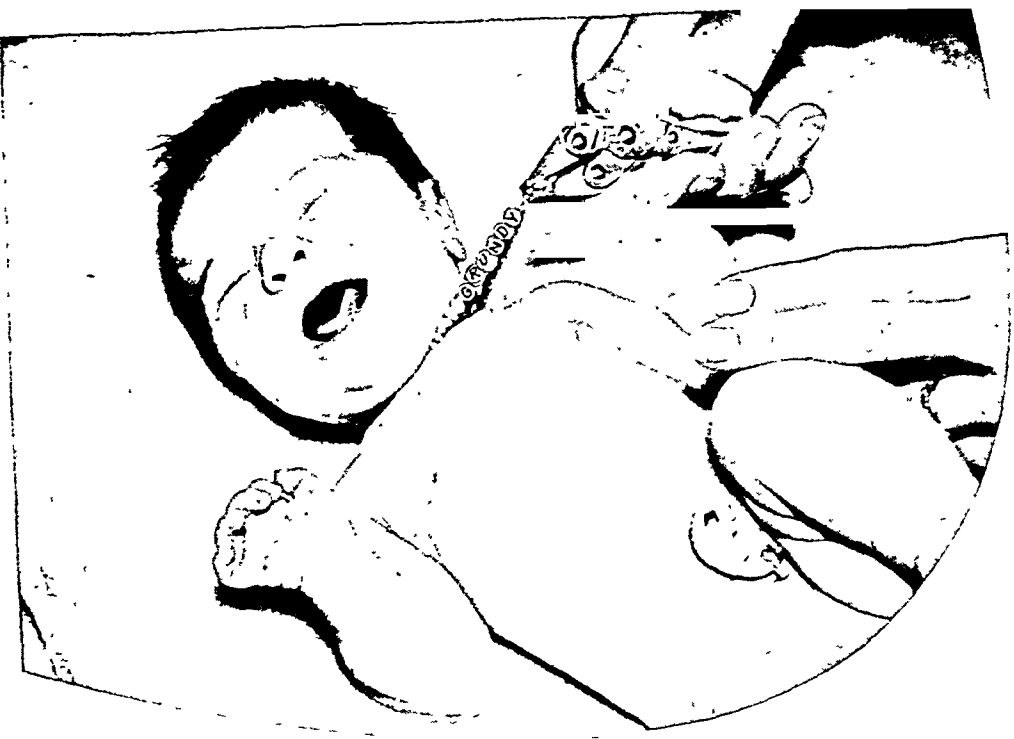
CRYSTALLINE PENICILLIN G SODIUM MERCK

MERCK & CO., Inc.

RAHWAY, N. J.

Manufacturing Chemists





Solomon Grundy

There are still too many Solomon Grundys—"born on Monday...died on Saturday"—for despite the gratifying decline in infant mortality, there is still only slight reduction in the number of deaths of infants under one month. To better an infant's chance of survival, the first feedings—and the right formula—can do much to minimize the early hazards to life.

'Dexin' has proved an excellent "first carbohydrate" because of its high dextrin content. It (1) resists fermentation by the usual intestinal organisms; (2) tends to hold gas formation, distention and diarrhea to a minimum, and (3) promotes the formation of soft, flocculent, easily digested curds.

Simply prepared in hot or cold milk, 'Dexin' brand High Dextrin Carbohydrate is well taken and well retained. 'Dexin' does make a difference.

HIGH DEXTRIN CARBOHYDRATE

'Dexin'

BRAND

Composition—Dextrins 75% • Maltose 24% • Mineral Ash 0.25% • Moisture 0.75% • Available carbohydrate 99% • 115 calories per ounce • 6 level packed tablespoonfuls equal 1 ounce • Containers of twelve ounces and three pounds • Accepted by the Council on Foods and Nutrition, American Medical Association. 'Dexin' Reg. Trademark

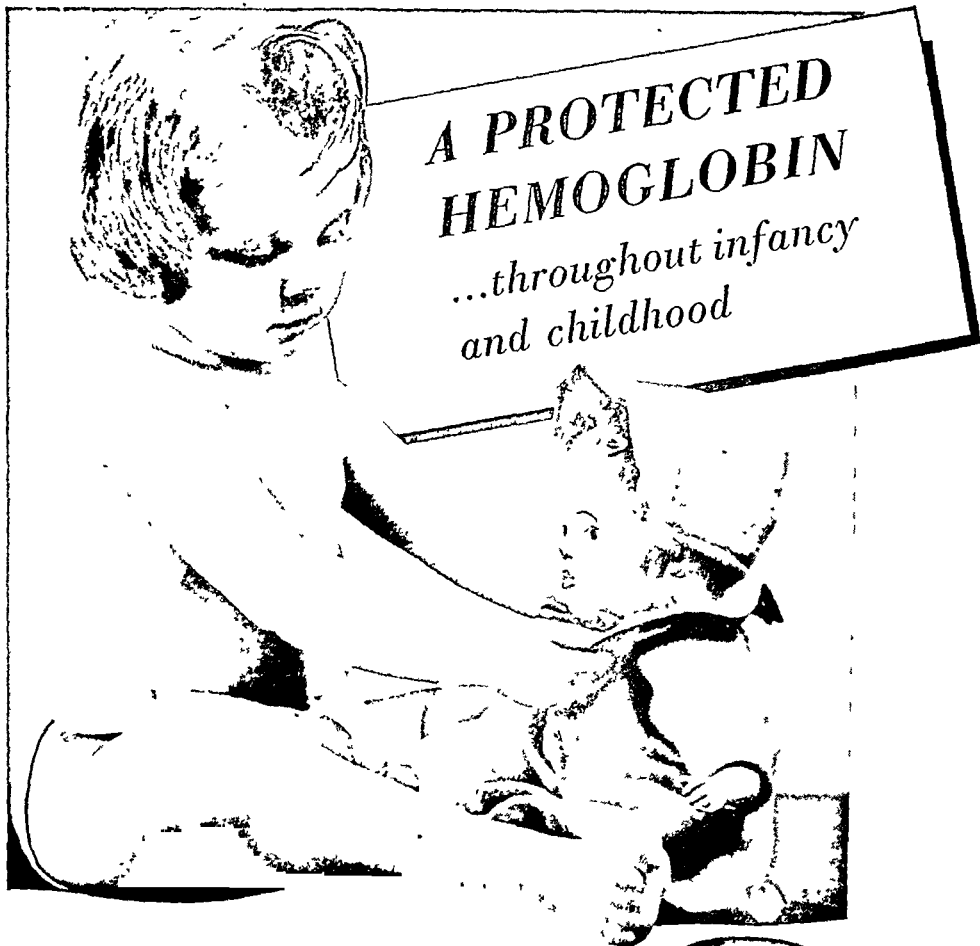
Literature on request



BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9 & 11 East 41st St., New York 17, N. Y.

April, 1948

Page 29



A PROTECTED HEMOGLOBIN

...throughout infancy
and childhood

During the early years of life the expanding blood volume makes heavy demands upon iron stores to satisfy hemoglobin requirements.

Copperin "B" promptly replenishes these inroads upon iron reserves — protecting the hemoglobin levels. Due to the presence of the catalyzing copper sulphate *all* of the iron ammonium citrate is available for use. Hence, the iron is present in very small quantity—32 Mg. per capsule. Copperin is well tolerated, causes no stomach irritation and being water soluble, may be taken in fruit juices, milk or feeding formula.

Write for samples and pediatrician's literature

MYRON L. WALKER CO. INC.

Mount Vernon, New York



COPPERIN

Q: Why do Pediatricians recommend Ry-Krisp for children?

A: Because it is crisp whole-grain bread, low in carbohydrates and fats. For these reasons—

Ry-Krisp stimulates teeth and gums
Because it's crisp, Ry-Krisp provides the teeth and gum exercise children need. Good for youngsters in the "teething age," too.

Satisfies between-meal hunger
Only whole-grain rye, salt, and water in Ry-Krisp. Doesn't spoil regular mealtime appetites, because it is low in carbohydrates. Yet, Ry-Krisp supplies the protein, minerals, and B complex vitamins of whole rye. Its tempting flavor means good eating, too.

Keep Ry-Krisp in mind for your young patients

FREE TO YOU

Allergy Diets—Wheat-free, Egg-free, Milk-free, Wheat-Egg-Milk-free and Restricted Diagnostic. Send for booklet containing single copies so you may order free diet pads as needed. Use coupon below.



RALSTON PURINA COMPANY, Nutrition Service
JP-G Checkerboard Square, St. Louis 2, Missouri.

Please send, no cost or obligation: C2143 Allergy Diets Booklet.

Name.....M.D.

Street.....

City.....Zone.....State.....

the preferred

PERTUSSIS IMMUNE SERUM—*human* IN VACUUM-DRIED FORM



This serum—established as the agent of choice in the treatment of, and passive immunization against, whooping cough—is now available to physicians everywhere.

Vacuum dehydration by the 'LYOPHILE' process provides high stability (a 5-year dating) and permits optimal concentration.

Standard price: \$6.50 per dose,

i.e., vial containing 20 cc. of serum, vacuum-dried.

3 to 4 doses generally required in treatment.

24-hour service to handle telegraphic orders.

For literature and full information, write to:

The **PHILADELPHIA
SERUM**

EXCHANGE *A Non-profit Organization*

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
1740 Bainbridge Street, Philadelphia 46, Pennsylvania



Pediatricians and geriatricians agree upon the need for prompt control of cough because its effects are particularly exhausting upon the child and the aged.

D

the preferred

PERTUSSIS IMMUNE SERUM—*human* IN VACUUM-DRIED FORM



This serum—established as the agent of choice in the treatment of, and passive immunization against, whooping cough—is now available to physicians everywhere.

Vacuum dehydration by the 'LYOPHILE' process provides high stability (a 5-year dating) and permits optimal concentration.

Standard price: \$6.50 per dose,

i.e., vial containing 20 cc. of serum, vacuum-dried.

3 to 4 doses generally required in treatment.

24-hour service to handle telegraphic orders.

For literature and full information, write to:

The **PHILADELPHIA
SERUM**

EXCHANGE *A Non-profit Organization*

THE CHILDREN'S HOSPITAL OF PHILADELPHIA
1740 Bainbridge Street, Philadelphia 46, Pennsylvania

Q: What food can solve one of your warm-weather feeding problems?

A: *Instant Ralston. It cooks in 10 seconds, so mothers find it easy to prepare—assuring your young patients a hot, nourishing cereal during summer months.*

Instant Ralston is whole wheat with added wheat germ. Provides energy for increased summer activities. Gives the advantages of hot cereal as an aid to digestion—sense of well-being.

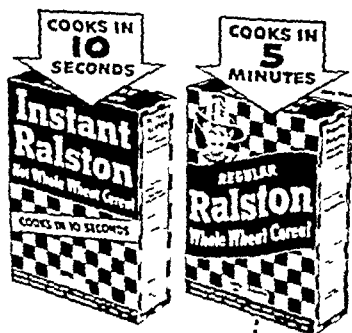
Supplies extra thiamine, extra protein . . . because it's $2\frac{1}{2}$ times as rich in wheat germ as whole wheat. And wheat germ is one of the best food sources of thiamine, which helps boost lagging summer appetites. Wheat germ provides, too, protein of biological value comparable to meat, milk and cheese proteins.

Good reasons for suggesting Instant Ralston this summer

Free

Feeding Direction Forms for four age groups: birth to 3 months; 3 to 6 months; 6 to 10 months; over 10 months.

Easy to use. Adaptable. Available in pads of 50 each, imprinted with your name and address if you wish.



USE THIS COUPON!

Ralston Purina Company, Nutrition Service
JP-7 Checkerboard Square, St. Louis 2, Mo.
Please send, no cost or obligation, samples of
Feeding Direction Forms, C848, so I may
order pads as needed.

Name _____
Address _____ M.D.
City _____
Zone _____ State _____



POSTSURGICALLY, and during convalescence in general, candy is a welcome "bright spot" in the sickroom.

First of all, it gives the patient a psychic stimulus which few other foods can give. For candy is more than merely food—it embodies a bit of the joy of living which every physician desires for his patient, which every patient needs to hasten recovery.

Second, the sugars in candy are readily utilized and calorically valuable, at a time when calories mean so much in the therapeutic regimen.

Third, many of the confections appreciated in the sickroom are those in the manufacture of which fruits, eggs, milk and cream are used. To this extent they contribute biologically adequate protein, vitamins, and minerals.

**NATIONAL
CONFECTIONERS'
ASSOCIATION**
COUNCIL ON CANDY OF THE

1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS

Whatever you call it...

POISON OAK SHRUB
in the West



POISON IVY VINE
in the East

...it's POISON to HIM!!

Whether it's POISON OAK or POISON IVY
Here are two things you can do—

Prevent it — CUTTER POISONOK*

When your sensitive patients are sensible and ask for protection—a pre-seasonal course of Cutter Poisonok, administered orally, gives the average person protection from 3 to 8 months—and oral administration is much the preferred method of desensitization. It allows you to adjust drop dosage for individual needs—and offers a simple method of prescription for home use. For the refractory case, Cutter will prepare special stronger concentrations, at your request, to enable you to give even the problem-patient protection.

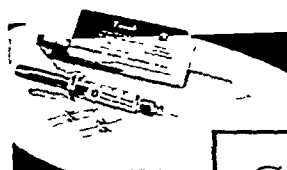
*To satisfy both sides of the Rockies, Cutter produces two purified extracts: Poisonok (oral) and Toxok (injection), made from poison oak leaves gathered in the West—and Poisonii and Toxiii, from Eastern ivy leaves.



Treat it — CUTTER TOXOK*

When the rash appears Cutter Toxok produces dramatic relief of symptoms. One or two 1 cc. intramuscular injections at 12 to 24 hour intervals stops the spreading eruption and reduces swelling and inflammation.

When injections are impractical for the patient, or if the case is mild, Cutter Poisonok is also a specific for treatment.



For literature, write
Dept. 34
Cutter Laboratories,
Berkeley 1, Calif.

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LABORATORIES
Berkeley 1, Calif.

CUTTER.
Fine Biologicals and
Pharmaceutical Specialties

Here's the sulfadiazine
that children actually like to take

Children
have
no
reluctance
in
taking



Eskadiazine

Exceptionally flavorful, this fluid sulfadiazine is the ideal dosage form for your young patients. They take it willingly because it tastes good. And it relieves tired parents and busy nurses of the chore of crushing tablets and coaxing a sick child to swallow an unappealing mixture.

Important, too, is the more rapid absorption of Eskadiazine. Flippin and associates* have established that desired serum levels are attained in two hours, rather than the six hours required for sulfadiazine in tablet form.

Eskadiazine

*Am. J. M. Sc. 210:111, 1915

*Smith, Kline
& French
Laboratories,
Philadelphia*

the outstandingly palatable fluid sulfadiazine for oral use

578... and piling up!

Inquiries being received from hospital administrators, staff members and public health officials evidence the nation-wide interest in the health potential of the "American" engineered

MILK FORMULA LABORATORY SERVICE

CHECK THESE IMPORTANT HIGHLIGHTS based on the newer knowledge of milk formula technic—

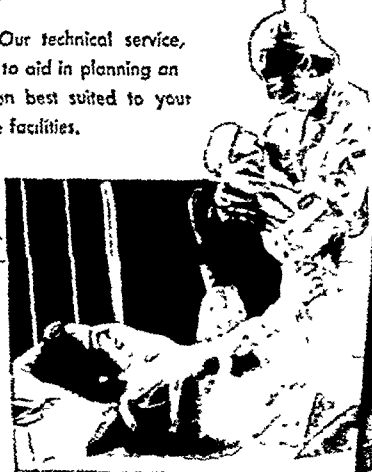
Provides a complete, progressive routine from returned, used bottles to the next infant feeding . . . with efficiency, speed and safety.

Provides all equipment necessary for the establishment of an aseptic technic.

Adaptable to institutions with requirements of from only 72 bottles per day up to unlimited volume.

GRATIS—Our technical service, qualified to aid in planning an installation best suited to your available facilities.

Recognizing that diarrheal diseases constitute one of the major preventable causes of infant morbidity and mortality . . . that facilities and equipment designed to insure freedom of contamination of infants' foods and supplies marks a dramatic advance in medical asepsis . . . installations are now being made in many institutions of both large and small volume requirements.



WRITE TODAY for complete details

AMERICAN STERILIZER COMPANY
Erie, Pennsylvania

DESIGNERS AND MANUFACTURERS OF SURGICAL STERILIZERS, TABLES AND LIGHTS



6

IMPORTANT ADVANTAGES in the management of urinary tract infections

Mandelamine* has gained increasing recognition as a urinary antiseptic of choice, because it offers six significant advantages:

- 1 prompt response**—Clinical experience shows that sterilization of urine is often secured within three to six days.
- 2 clinical effectiveness**—Carefully analyzed studies have demonstrated a high proportion of successful results—74 per cent in one series of 200 cases,¹ and 83 per cent in another series of 63 cases.²
- 3 wide range of antibacterial action**—MANDELAMINE is effective against bacteria most frequently encountered in common infections of the urinary tract.
- 4 safety**—Administration of MANDELAMINE involves virtually no risk of toxic reactions, thus eliminating need for careful selection of patients or close supervision.
- 5 simplicity**—MANDELAMINE therapy is uncomplicated—no accessory acidification, usually . . . no dietary restriction . . . no fluid regulation.
- 6 acceptability**—Cooperation of the patient is readily secured because of convenience of therapy. Dosage is simple: 3 to 4 tablets orally, three times daily.

MANDELAMINE

Reg. U. S. Pat. Off.

Brand of Hexydaline

(Methenamine Mandelate)

SUPPLIED: Enteric-coated tablets of 0.25 Gm. (3½ gr) each, in packages of 120 sanitaped tablets, and in bottles of 500 and 1,000.

1. Carroll, G., and Allen, N. H.: *J. Urol.* 55: 674 (1946).

2. Kirwin, T. J., and Bridges, J. P.: *Am. J. Surg.* 52: 477 (1941).

*The word MANDELAMINE is a registered trademark of Nepers Chemical Co., Inc.



NEPERA CHEMICAL CO., INC.

Manufacturing Chemists

NEPERA PARK

YONKERS 2, N. Y.

Wyeth presents METHADON, the new and superior synthetic analgesic, in a standardized, stable dosage form for oral use in the direct and effective control of coughs of all types—

SYRUP ALTHOSE®

(SYRUP METHADON, WYETH)

SYRUP ALTHOSE is a dosage form of methadon particularly designed for the symptomatic relief of painful or debilitating and sleep-preventing coughs associated with bronchial or pulmonary infections, when such coughs interfere with adequate response to treatment or delay convalescence after the infection is under control.

Methadon resembles codeine in its action on coughs but is effective in very much smaller doses. In *Syrup Althose*, the powerful action of methadon is tamed down to a point of minimum side effects consistent with efficacy. Nausea or dizziness are uncommon. No effect has been noted upon blood pressure, respiration or heart rate. *Syrup Althose* does not act as a sedative, excepting in those cases in which cough has kept patients awake for some time previously. Unlike morphine or other opium derivatives, the action of methadon, as exhibited in *Syrup Althose*, is not hypnotic.

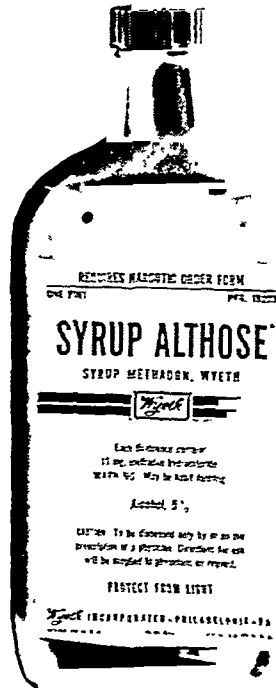
It has three advantages: (1) Its action is specific and does not diminish with use. (2) It has unusual palatability. Patients appreciate the delicate flavor. (3) Properly prescribed, it will not impair appetite nor upset digestion.

DOSAGE: One teaspoonful of *Syrup Althose*, containing only 1.25 mg. (1/50th grain) is sufficient to exert antitussive action in most simple bronchial irritations of adults. One to two teaspoons every 3 or 4 hours insure a degree of comfort even in more severe infections.

SYRUP ALTHOSE is a 1:3000 solution (one-sixth grain or 10 mg. per fl. oz.) in a palatable syrup of suitable pH of 6-dimethyl-amino-4, 1-di-phenyl-3-heptanone hydrochloride, formerly known as Amidone and recently named methadon by the Council on Pharmacy of the American Medical Association.

WARNING: may be habit-forming. Until more evidence is available as to the habit-forming properties of methadon in small doses, *Syrup Althose* must be prescribed on narcotic forms. Large doses of methadon can lead to addiction in predisposed individuals. The phy-

sician should therefore make certain that the patient does not overdose. On the other hand, therapeutic doses given for control of the cough reflex have no perceptible effect on the digestive tract or on sensitivity to pain, and the development of tolerance has not been reported.



Philadelphia 3, Pa.

When Should Good Nutrition Step In?

No one deliberately skips his evening meal, and few persons forego luncheon. But a significantly large number of adults and even children of school age fail to eat breakfast entirely or eat a totally inadequate breakfast. Yet this failure to eat a nutritionally sound breakfast makes it almost impossible for the other two meals of the day to supply the nutrients required daily by the organism. Hence good nutrition should start with breakfast.

To serve as a foundation for planning the morning meal, a basic breakfast pattern consisting of fruit, cereal, milk, bread and butter has been widely advocated. It provides a well-rounded assortment of essential nutrients, is universally available, is remarkably economical, and is readily acceptable to both children and adults.

The cereal serving, consisting of hot or ready-to-eat breakfast cereal, milk, and sugar, is the centerpiece of this meal. It supplies high quality protein, readily utilized caloric food energy, B-complex and other vitamins, and important minerals. In addition, it affords almost endless variety.

The table indicates the nutrient values of this basic breakfast and the contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk and 1 teaspoonful of sugar.



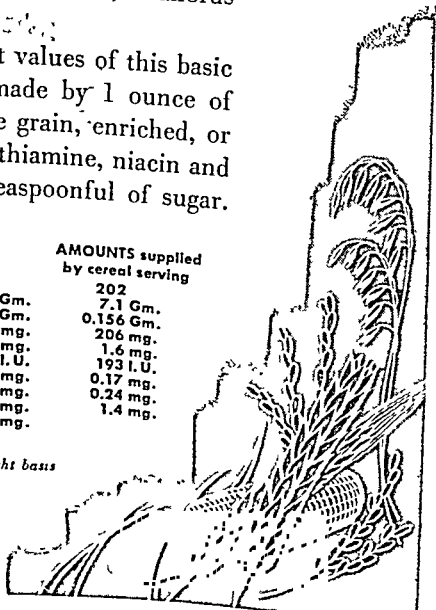
The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

BASIC BREAKFAST	TOTALS supplied by Basic Breakfast	AMOUNTS supplied by cereal serving
Orange juice, 4 oz ;		202
Ready-to-eat or		7.1 Gm.
Hot Cereal, 1 oz. ;	CALORIES..... 611	0.156 Gm.
Whole Milk, 4 oz ;	PROTEIN..... 20.7 Gm.	206 mg.
Sugar, 1 teaspoon;	CALCIUM..... 0.465 Gm.	1.6 mg.
Toast (enriched,	PHOSPHORUS .. 488 mg.	193 I.U.
white), 2 slices;	IRON..... 3 mg.	0.17 mg.
Butter, 5 Gm.	VITAMIN A..... 1074 I.U.	0.24 mg.
(about 1 teaspoon);	THIAMINE..... 0.52 mg.	1.4 mg.
Whole Milk, 8 oz.	RIBOFLAVIN..... 0.87 mg.	
	NIACIN..... 2.3 mg.	
	ASCORBIC ACID .. 64.8 mg.	

*Composite average of all breakfast cereals on dry weight basis

CEREAL INSTITUTE, INC.

A research and educational endeavor devoted to the betterment of national nutrition.
135 South La Salle Street • Chicago 3



The Doctors' Album of New Mothers

No. 21: SCARY MRS. SPALDING



Right from the first, Mrs. S. was a grade-A alarmist. The hospital corridors resounded: "Help! My child's *cross-eyed*! Nurse! there's a dreadful *hollow spot* on the front of his head!"

And at home—same thing. Mrs. S.'s doctor learned to shudder when his nurse announced: "Mrs. Spalding on the phone." "Oh, doctor—baby *cries* so. It's a *symptom*, isn't it?" And, inevitably, "Doctor, he's got little red spots on his tummy! Is it chicken pox? Measles? Scarlet fever?"



Even calmer mothers than Mrs. Spalding get upset over the little external skin irritations so common to infants.

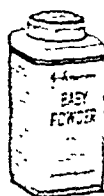
And so many doctors head off the "distress calls" before they start—by suggesting frequent sprinkles of Johnson's Baby Powder, soft, pure, borated, to help *prevent* prickly heat and similar infant discomforts.

Gentle Johnson's Baby Powder is the choice of more doctors and nurses than all other brands put together.



JOHNSON'S BABY POWDER

Johnson & Johnson



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\$250

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Nurses report:

With Swift's Strained Meats "Babies were more satisfied ... slept better at night"*

In test feedings* the protein content of the formula of six-weeks-old infants was increased 25% by the addition of Swift's Strained Meats. The nursing staff felt that babies who received Swift's Strained Meats were *more satisfied and slept better* than the control babies. In the opinion of the pediatrician in charge, meat-fed babies were *in a better physical condition* as a result of the meat supplement. This study indicated further that meat not only checks the drop in

hemoglobin, characteristic of babies at this early age, but actually promotes hemoglobin and cell formation.

**100% meats — fine enough
for formula-feeding**

Specially prepared, soft and smooth, Swift's Strained Meats facilitate introducing meat *earlier in life*. They provide an excellent, palatable source of complete, high-quality proteins needed to support the infant's rapid growth. Swift's Strained Meats also furnish goodly amounts of thiamine, niacin, riboflavin and iron — nutrients not ordinarily plentiful in the infant diet. The six kinds of Swift's Strained Meats differ in taste and texture from baby's other solid foods — offer new flavor experiences that help him form nutritionally sound eating habits. The variety includes: beef, lamb, pork, veal, liver and heart. For further information, write Dept. SMB, Swift & Company, Chicago 9, Illinois.

*MEAT IN THE DIET OF YOUNG INFANTS
Ruth M. Leeterton, Ph.D. and George Clark, M.D.
Journal of the American Medical Association
(J.A.M.A. 134:1215, August 9, 1947)

SWIFT & COMPANY • CHICAGO 9, ILLINOIS

SWIFT

...foremost name in meats

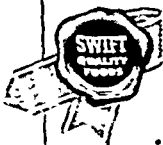
first with 100% Meats for Babies



All nutritional statements made in this advertisement are accepted by the Council on Food and Nutrition of the American Medical Association.

ALSO SWIFT'S DICED MEATS

Bite-size tender meats — firm enough to encourage chewing. Swift's Diced Meats offer tempting flavors that help prevent anorexia in the older baby and young child.



COMPLETE REMISSION

in
Aural
Infections

* DRAWS PLASMA TO SURFACE . . . * DISSOLVES NECROTIC TISSUE
* BACTERICIDAL, DEODORANT, DETERGENT, PEPTIZING, NON-TOXIC

Glycerite of Hydrogen Peroxide *ipoc* With Carbamide

* BIBLIOGRAPHY

Arch. Otolaryngol.,
43 605, 1946.
E., E., N., & T. Mo.,
26 27, 1947.
Laryngoscope,
56 556, 1946.
New Eng. J. Med.,
234 468, 1946.
Annals of Allergy,
4 33, 1946.
J. A. Ph., A. (Sc. Ed.)
35 304, 1946.
Literature on request.

Clinical studies concerned with the use of Glycerite of Hydrogen Peroxide in the treatment of chronic purulent otitis media demonstrated seventeen of twenty-nine patients in complete remission in 14 days and the remainder by the 38th day. The patients studied presented conditions existent for periods of 2 weeks to over 40 years. Previous treatment by the usual therapeutic means, including tyrothricin or penicillin, was ineffective in all cases.

Constituents:

Hydrogen Peroxide 1.446%, Urea (Carbamide) 2.554%, 8 Hydroxyquinoline 0.1%.
Dissolved and stabilized in substantially anhydrous glycerol . . . q.s. ad. 30cc.

Available on prescription in one-ounce bottle with dropper
Administration One half dropperful two to four times daily

International PHARMACEUTICAL
132 NEWBURY STREET, BOSTON

ORATION

WHEN SENSITIVITY TO COW'S MILK LACTALBUMIN IS SUSPECTED

Meyenberg Evaporated GOAT MILK

THE SUPERIOR-QUALITY
NATURAL MILK FOR
INFANTILE ECZEMA
AND DIFFICULT
FEEDING CASES



PRODUCTS

MEYENBERG Evaporated Goat Milk has gained outstanding national acceptance because it is *uniform, sterile and more palatable*. Prescribe or recommend Meyenberg whenever Cow's Milk allergy is suspected.



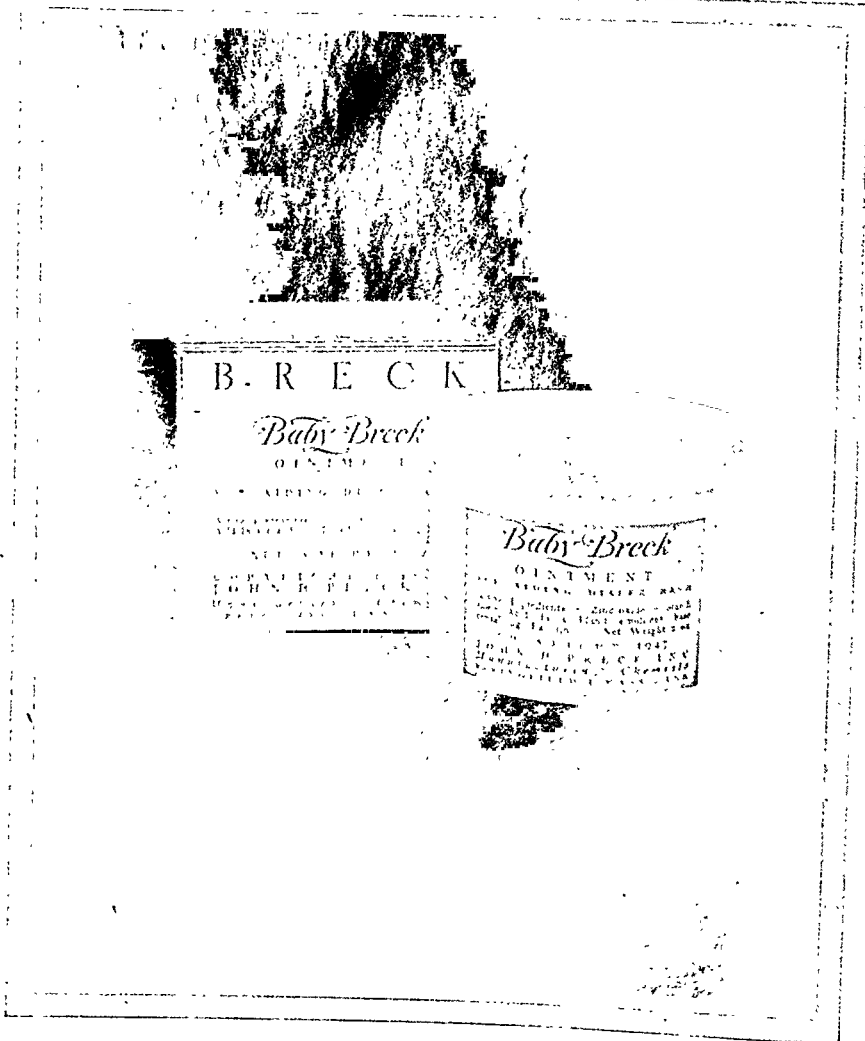
Available in 14-ounce hermetically-sealed containers
at all pharmacies

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Available
in
Unlimited
Quantities

Advertised only to
the medical profession

SPECIAL MILK PRODUCTS, INC.

11500 TENNESSEE AVENUE • LOS ANGELES 25, CALIFORNIA



Baby Breck

O I N T M E N T For Aiding Diaper Rash

Baby Breck Ointment helps to prevent and eliminate diaper rash. A bland ointment with a minimum allergic reaction is often necessary at diaper changes to protect the extra sensitive skin of babies. Baby Breck Ointment contains lanolin and may be used on other chafed areas of the skin.

JOHN H BRECK INC • MANUFACTURING CHEMISTS • SPRINGFIELD 1 • MASSACHUSETTS
CANADIAN ADDRESS • 310 SLATER STREET • OTTAWA

**from the third week of life
to adolescence...**



The simplicity and convenience of using milk diffusible Drisdol in Propylene Glycol facilitate patient cooperation from early infancy to adolescence.

An average daily dose of 2 drops in milk for infants and from 4 to 6 drops for children provides effective low-cost vitamin D protection throughout the critical years of growth and development.

Available in bottles of 5, 10 and 50 cc. with special dropper delivering 250 U.S.P. units per drop.

DRISDOL IN PROPYLENE GLYCOL
MILK DIFFUSIBLE VITAMIN D PREPARATION
ODORLESS • TASTELESS • ECONOMICAL



DRISDOL, trademark reg
U. S. Pat. Off. & Canada,
brand of crystalline vitamin D₂
(calciferol) from ergosterol

Winthrop Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

DESITIN OINTMENT

PIONEER IN THE FIELD OF

EXTERNAL COD-LIVER OIL THERAPY

USED EFFECTIVELY IN THE TREATMENT OF Wounds, Burns, Ulcers, especially of the Leg, Intertrigo, Eczema, Tropical Ulcer, also in the Care of Infants.

Desitin Ointment contains Cod-Liver Oil, Zinc Oxide, Petrolatum, Lanum and Talcum. The Cod-Liver Oil, subjected to a special treatment which produces *stabilization* of the Vitamins A and D and of the unsaturated fatty acids, forms the active constituent of the Desitin Preparations. The first among cod-liver oil products to possess unlimited keeping qualities, Desitin, in its various combinations, has rapidly gained prominence in all parts of the globe.

Desitin Ointment is absolutely non-irritant; it acts as an anti-phlogistic, allays pain and itching; it stimulates granulation, favors epithelialisation and smooth cicatrisation. Under a Desitin dressing, necrotic tissue is quickly cast off; the dressing does not adhere to the wound and may therefore be changed without causing pain and without interfering with granulations already formed; it is not liquefied by the heat of the body nor in any way decomposed by wound secretions urine, exudation or excrements.

DESITIN POWDER

Indications: Minor Burns, Exanthema, Dermatitis, Care of Infants, Care of the Feet, Massage and Sport purposes.

Desitin Powder is saturated with cod-liver oil and does not therefore deprive the skin of its natural fat as dusting powders commonly do. Desitin Powder contains Cod-Liver Oil, (with the maximum amounts of Vitamins and unsaturated fatty acids) Zinc Oxide and Talcum. Professional literature and samples for Physicians' trial will be gladly sent upon request.



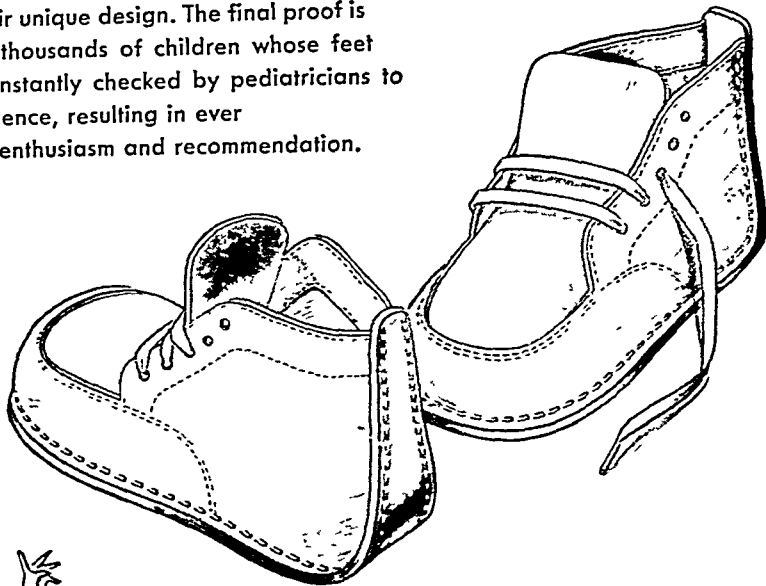
Sole Manufacturer and Distributor in U.S.A.
DESITIN CHEMICAL COMPANY
70 SHIP STREET • PROVIDENCE • RHODE ISLAND

Why Pediatricians Recommend

JUMPING-JACKS
SOFT SHOES FOR HARD WEAR

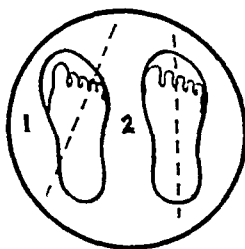
For Childrn 6 Months to 4 Years Old

The Superiority of Jumping Jack shoes for youngsters is evident in their unique design. The final proof is in the countless thousands of children whose feet have been constantly checked by pediatricians to justify their confidence, resulting in ever increasing enthusiasm and recommendation.



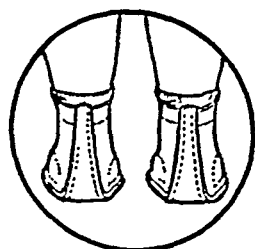
Exclusive Patented Extension Sole

No other shoe offers this innovation in construction—a single piece of leather from toe to top of shoe—with all seams on the outside—no striking edges that wear and influence walking habits.



Prevents Friction Retains Shape

Figure 1 (left) shows pressure resulting in cramped foot, friction due to conventional shoe. Figure 2 (right) allows foot freedom, equal distribution of weight and flexibility.



Builds Confidence For "First Steps"

Patented, Jumping Jack support helps prevent ankles from turning . . . assures correct, healthful walking from the start. And excellent materials and craftsmanship afford extra satisfaction.

VAISEY-BRISTOL SHOE COMPANY, INC.
625 SO. GOODMAN STREET • ROCHESTER 7, N. Y.



A BABY

SCENE I

*"a thin, pale . . .
restless, whining
infant refusing part
of its formula . . ."*



SAME BABY
Time: 2 weeks
later

SCENE II

*—now "a happy, rosy-cheeked,
smiling baby whose appetite
never seemed completely
satisfied and whose gain in
weight was remarkable."*



Between the scenes, this dramatic change was achieved with vitamin B therapy.¹ The lack of appetite from which the baby suffered is a serious matter in infancy, and one of the commonest problems in pediatrics. Many doctors now prescribe 'Ryzamin-B' No. 2 to combat infant anorexia. Its rich vitamin B content provides the needed appetite stimulation: the convenience with which it may be administered in formula or fruit juice makes it especially adaptable to pediatric needs.

Older children enjoy 'Ryzamin-B' No. 2 from the special measuring spoon, as a delicious spread when mixed with jam or peanut butter, or dissolved in milk, fruit juice or other beverages. Containing the natural B complex as a concentrate of *Oryza sativa* (American rice) polishings, 'Ryzamin-B' No. 2 also supplies potent synthetic B factors.

'RYZAMIN-B' BRAND RICE POLISHINGS CONCENTRATE NO. 2

WITH ADDED THIAMINE HYDROCHLORIDE, RIBOFLAVIN AND NICOTINAMIDE
TUBES OF 2 OZ. AND BOTTLES OF 8 OZ

1. Hoebler, B. P., Quoted In Foss's Foundation of Nutrition, N. Y., Macmillan Co., 1933, p. 273. • 'Ryzamin-B' reg. trademark



BURROUGHS WELLCOME & CO. (U.S.A.) INC., 9 & 11 EAST 41ST STREET, NEW YORK 17

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**MODERN, EFFICIENT
SCIENTIFICALLY CORRECT**

This "Histacount" form meets the needs of one branch of the Medical Profession. There is a "Histacount" form for every branch. All are basically identical and can be used together where one doctor covers two or more specialties. All are scientifically correct, up-to-the-minute and amazingly efficient. All are made for standard cards files 5" x 8" and 4" x 6".

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**MORE THAN 50,000 DOCTORS USE
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By John R. Harvin, M.D., W. D. Hastings, Jr., M.D., and C. R. F. Baker, M.D.,
Sumter, S. C.

VARICELLIFORM ERUPTION OF KAPOSI DUE TO VACCINIA VIRUS COMPLICATING ATOPIC ECZEMA.

By Joseph H. Fries, M.D., Stanford Borne, M.D., and Harold L. Barnes, M.D., Brooklyn,
N. Y.

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By Harold W. Bischoff, M.D., Adrian Recinos, Jr., M.D., William S. Anderson, M.D.,
and E. Clarence Rice, M.D., Washington, D. C.

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Samuel Livingston, M.D., Laslo Kajdi, M.D., and Edward M. Bridge, M.D., Baltimore, Md.

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By Leslie Paxton Barker, M.D., New York, N. Y.

**RELATIONSHIP OF RACE TO THE INCIDENCE OF DIPHTHERIA AND TO SCHICK, TUBERCULIN, AND
WASSERMANN TESTS IN HOSPITALIZED CHILDREN.**

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Original Communications

HUNGER EDEMA IN CHILDREN

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ATHENS, GREECE

INTRODUCTION

THE conditions created by the war and occupation of Greece resulted in the lack of many foodstuffs, particularly animal protein and fat, but also of such items as salt. This resulted in extensive hunger, which was more intense during the winter of 1941-1942 in the urban centers. Large sections of the working and urban middle classes were exposed to prolonged and severe undernourishment, the result of which was the appearance of nutritional edema. This involved at first the members of older age groups, more so the hard working manual laborers. Later on, younger age groups and children were also affected. This gave us the opportunity to secure some clinical and laboratory observations.

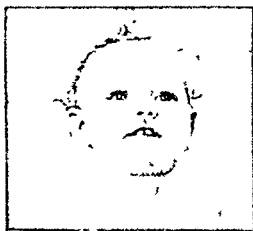
GENERAL CONSIDERATIONS

From Sept. 25, 1941, to Feb. 5, 1943, 106 children suffering from hunger edema were admitted to our service. In this group there were sixty-six boys and forty girls. It was of interest that nutritional edema appeared more frequently in males than in females.

Our patients came from the slum and tenement districts of the Athens area, several of them having been brought into the hospital by emergency teams who had found them in a miserable condition in the streets. The largest number of these patients (sixty-seven) was admitted during the October, 1941, to April, 1942, period. Of the total number, sixty-three belonged to the 1- to 3-year-old group which had passed the period of weaning from the breast. Above this age there was a lower incidence of hunger edema, probably due to gastrointestinal adjustment of the older children to the poor quality of food then available, with concomitant lower incidence of gastrointestinal disturbance.

We observed no hunger edema below the age of 6 months. This was probably due to the fact that young infants either received no mother's milk because of lack of supply and thus died, or received basal amounts of human milk and escaped hunger edema. Milk other than human was not available at that time.

From the First Pediatric Service of the Athens University School of Medicine.
This work is dedicated to the memory of Professor G. N. Makkas.



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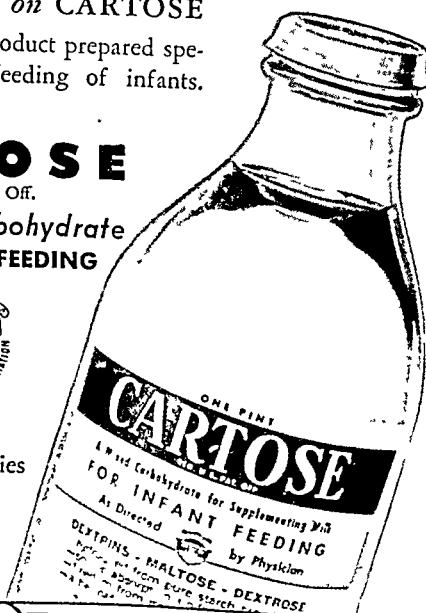
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Tuberculin tests after Mantoux were positive in dilution 1:10,000 in twenty-four out of 106 cases.

In spite of our efforts to secure more extensive laboratory studies, we found this impossible, due to lack of even the most elementary reagents.

The prognosis of this syndrome depends upon: (a) the degree of malnutrition; (b) the co-existence or delayed appearance of complications; and (c) the possibility for correction of the nutritional status. Out of our 106 patients, eighty-one were cured (76.42 per cent) and twenty-five died (23.58 per cent). This mortality rate includes malnutrition and co-existing diseases. The disappearance of edema occurred in the uncomplicated cases during the first fourteen days and on the average on the thirteenth day of admission, following gradual restitution of food intake on the basis of age.

With reference to the pathogenesis of nutritional edema, several explanations have been forwarded. Of these the most widely quoted ones are: (1) the theory of altered capillary permeability due to lipid deficiency, lipoids being essential for capillary function; (2) the excessive salt and water intake with storage of both in the tissues; and (3) hypoproteinemia.

HYPOPROTEINEMIA AND HUNGER EDEMA

The purpose of this investigation has been the establishment of: (1) the immediate relationship of hunger edema to the diminution of total serum protein (TSP) below normal levels; (2) the immediate effect of animal protein on the re-establishment of normal TSP values, (3) the immediate effect of re-establishment of the normal TSP values on edema.

We specifically investigated forty out of the 106 patients with these aims in mind. These patients we divided in three groups: Group A, comprising thirty-three children in whom we determined the serum proteins during the period of qualitative and quantitative nutritional improvement until the good or bad outcome; Group B, comprising four children in whom we investigated the effect of food containing normal amount of calories free from animal protein on the TSP level; Group C, comprising three children in whom we investigated the effect of special animal proteins on the re-establishment of normal serum protein levels by using milk, egg white, and egg yolk.

To complete the observations and to verify our impressions we produced nutritional edema in a group of three normal children by withholding animal protein from the diet.

The determinations of TSP were done by the refractometric method of Robertson. This method is simple, quick, and easy but has the disadvantage of being influenced by abnormally high urea, lipid, and sugar concentrations in the blood. In our cases, however, these substances, with possible exception of fat, were encountered in subnormal amounts. We believe, therefore, that our results can be considered as accurate.

Group A.—The TSP after admission of thirty out of thirty-three patients was determined (a) on twelve during the first day (b) on thirteen during the second, and (c) on five during the third day. The values of TSP were as follows: subgroup (a) had an average of 4.42 and in six cases was below 4.0 Gm. per 100

CLINICAL PICTURE

Infants and children with nutritional edema presented the following clinical picture in our subjects:

There was pallor, marked emaciation, delayed development (particularly in the case of infants), prostration, disappearance of the subcutaneous adipose-areolar tissue, wasting of the muscle masses, and edema. The edema appeared first over the dorsal surfaces of the feet and the ankles and then progressed insiduously to appear over the dorsal surfaces of the hands and over the eyelids. Gradually the edema extended from the ankles to the legs and thighs, from the hands to the forearms and arms, and from the eyelids to the rest of the face. The excessive swelling of the involved parts was in striking contrast to the emaciated edema-free regions of the body. In more severe cases there was extension of the edema to the external genitalia, rising up to the lumbar region. In very severe cases it was generalized. In the case of a 17-month-old boy there was excoriation of the epidermis with oozing of serous fluid. Ascites, hydrothorax, and hydropericardium were often encountered. The body weight of the infants was definitely diminished in spite of the edema, due to severe changes in general nutrition.

The edema was of the pitting type and doughy in nature. It had a tendency to reappear after having responded to nutritional measures, usually in connection with gastrointestinal disturbances.

The overlying skin was shiny, pale or bluish red. We observed frost-bites over the affected areas with ulceration in two patients and with gangrene of nose and one big toe in one patient. A fine desquamation of the epidermis particularly over the chest was seen repeatedly. Furunculosis was common, and on some rare occasions we observed hemorrhagic macules and bruises (seven children). Pellagroid rash was found over the extremities of four patients, due to co-existing avitaminosis.

Ophthalmological examination revealed xerophthalmia in three children and keratomalacia in one. The co-existing rachitic manifestations were attributed to pre-existing vitamin D deficiency.

Hypothermia was a common sign.

The lungs showed bradypnea with wet râles over the bases and ronchi over the rest of the field.

The cardiovascular system showed distant heart sounds, bradycardia, and hypotension.

Gastrointestinal disturbances were common. Nine patients had diarrhea stools, fourteen had mucous ones, and in four mucosanguineous excreta were encountered.

The urinary system showed polyuria and evidence of renal irritation in ten cases.

The nervous system was free from abnormal manifestations and the sensorium was clear even in the severest cases.

The blood showed moderately low red blood cell counts, low hemoglobin, leucopenia with lymphocytosis, and severe hypoproteinemia with low blood urea.



Fig. 3—Showing edema and skin rash.



Fig. 4—Showing edema, skin rash, and emaciation.



Fig 1—Showing edema and skin rash



Fig 2—Showing edema and skin rash

c.c.; subgroup (b) had 4.37 Gm. per 100 c.c. on the average; subgroup (c) had 4.94 Gm. per 100 c.c. on the average. In relation to age, subgroup (a) included seven patients from 9 months to 3 years who averaged 4.56 Gm. per 100 c.c. and five patients from 4 to 10 years who averaged 4.24 Gm. per 100 c.c.. In subgroup (b), ten children were 10 months to 3 years old and had an average TSP of 4.45 Gm. per 100 c.c.; three children were 4 to 8 years old and averaged a TSP of 4.12 Gm. per 100 c.c. In subgroup (c) there were five patients 22 months to 3 years old who had average TSP of 4.94 Gm. per 100 c.c.

These observations reveal that (1) the TSP was considerably below normal (5.90 Gm.) on admission, with the exception of two children who were low normal. In all the others (twenty-eight) TSP was below normal, ranging from 2.84 Gm. per 100 c.c. to 5.68 Gm. per 100 c.c. (2) The higher serum proteins in the cases of children from 9 months to 3 years of age as compared to the 4- to 10-year-old children is probably due to the fact that larger amounts of animal protein had been administered to the younger children in the form of milk.

These thirty-three children were given gradually increasing doses of food orally until the optimum was reached. During this period we determined the TSP repeatedly. The determinations showed continuously increasing values which reached normal levels within eleven to twelve days on the average. At the same time there was a parallel decrease in body weight with diminution of the edema, which disappeared in thirteen to fourteen days. This demonstrates the relationship between normal food intake and TSP on the one hand, and TSP level and edema on the other.

Group B.—The effect of animal protein on hunger edema was investigated in four children who were given no animal protein. In three of these, animal protein was withheld for thirteen, sixteen, and nine days, respectively. This time period was adequate to reduce the edema in the patients of the previous group, who received a complete diet. The animal protein-free food which was otherwise complete in terms of other foodstuffs, caloric contents, and was supplemented by vitamins, had little effect on the serum protein level of the two first children while in the third there appeared a diminution of TSP from 4.92 to 3.94 Gm. per 100 c.c. The body weight diminished to some extent in the first child (8 years old), with some amelioration of the edema, but remained stationary in the second (5 years old), and increased considerably in the third (3 years old), with aggravation of the edema.

These observations demonstrate the necessity for more animal protein in younger children. No gastrointestinal disturbance appeared in any of the patients.

Following the above specified periods of observation, animal protein (milk, eggs, cream) was added to the diet at the expense of carbohydrate and fat by keeping the caloric intake stable. Soon after the administration of animal protein there was a rapid and continuous increase of TSP. The latter reached normal levels with concomitant rapid loss of edema, which disappeared after serum levels reached normal. This is in contrast to the views forwarded by Maase and Zondek,¹² who attributed hunger edema to the lack of fat and lipid.

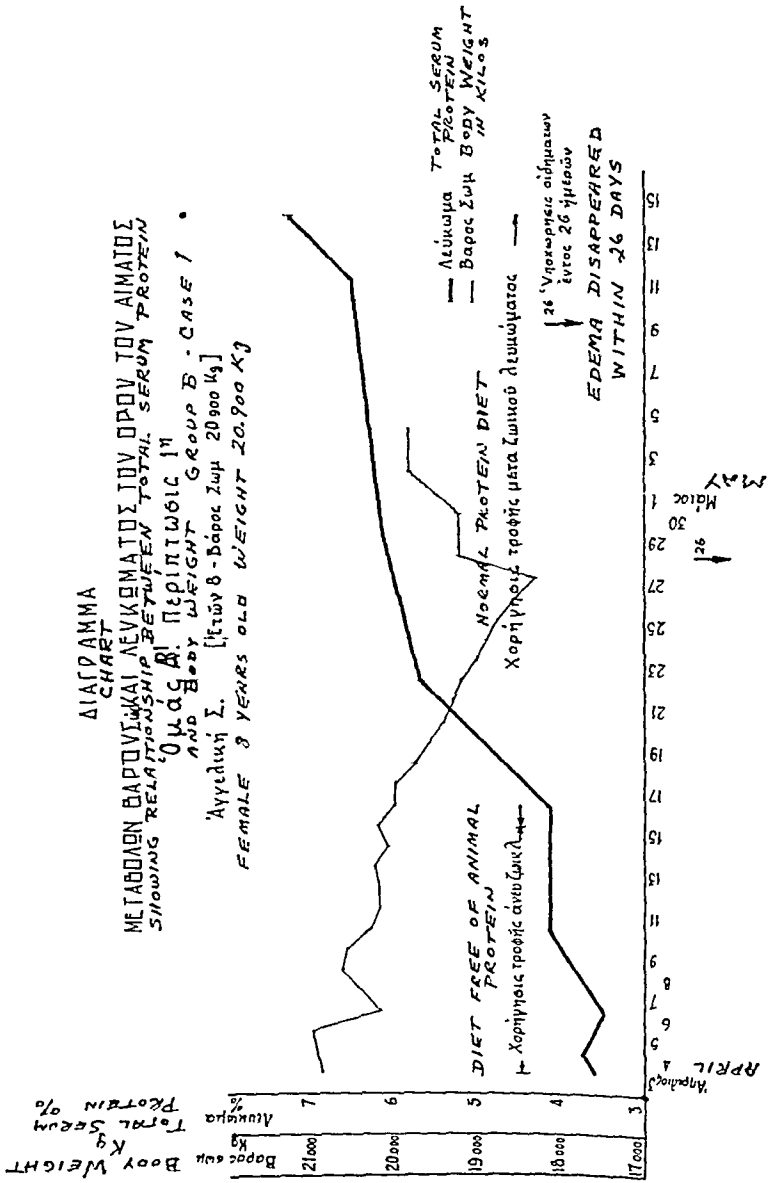


Chart I.—Illustrating Case 1, Group B.

In the fourth of these patients (aged 10) the patient received no animal protein but was given a high caloric intake high in vegetable protein. After the seventh day on this diet there appeared an increase in TSP with fall in body weight and diminution of edema. After fourteen days the TSP reached normal and the edema disappeared. This case demonstrates that older children can lose the edema when given large amounts of vegetable protein two or three times the equivalent amounts). It is noteworthy, however, that, although from the fifteenth to the twenty-third day the patient was on the same diet, his TSP diminished from 6.98 to 6.12 with concomitant increase in body weight, meaning probable water retention. After the twenty-third day he was given a lower caloric intake with added animal protein, which resulted in increase in total protein to 8.06, twenty days later. This was followed by amelioration of general nutrition and disappearance of edema.

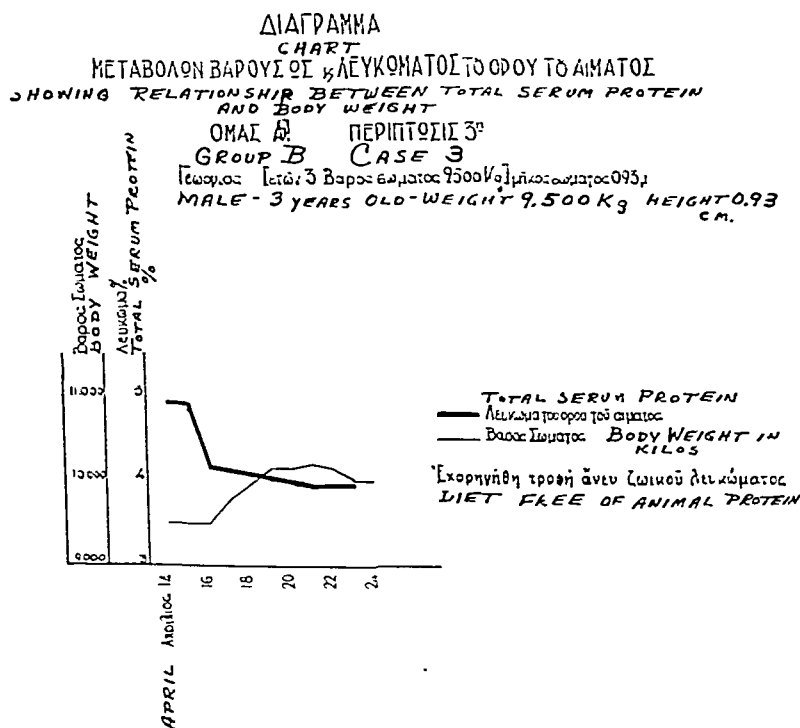


Chart III.—Illustrating Case 3, Group B.

Group C.—(Three cases) The first patient received milk and sugar in amounts covering the caloric needs for weight and age for eleven days. The amount of protein was twice the required and that of carbohydrate and fat was normal. The second patient received ten egg whites prepared with sugar, containing adequate amounts of calories, markedly excessive protein, and small amount of carbohydrate for seventeen days. The third patient was offered five egg yolks daily and 75 Gm. of sugar, which made an adequate diet from caloric protein, carbohydrate, and fat viewpoint.

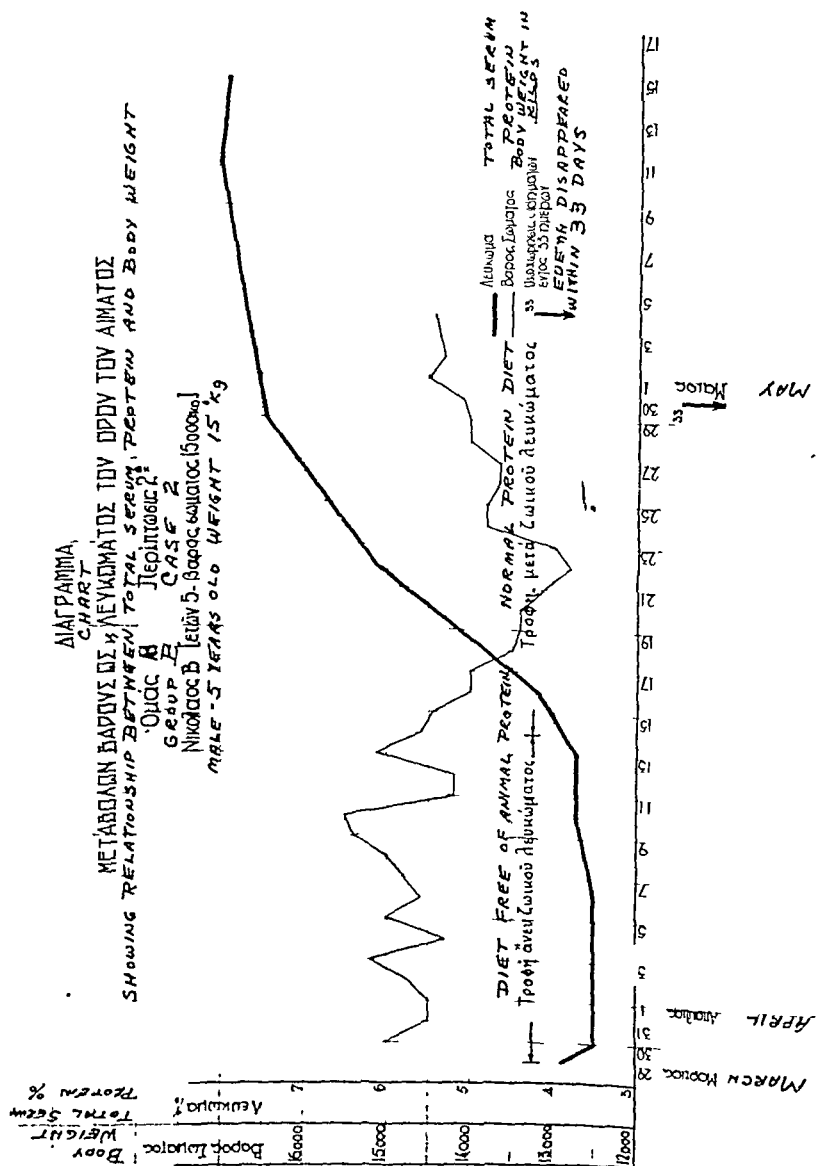


Chart II.—Illustrating Case 2, Group B.

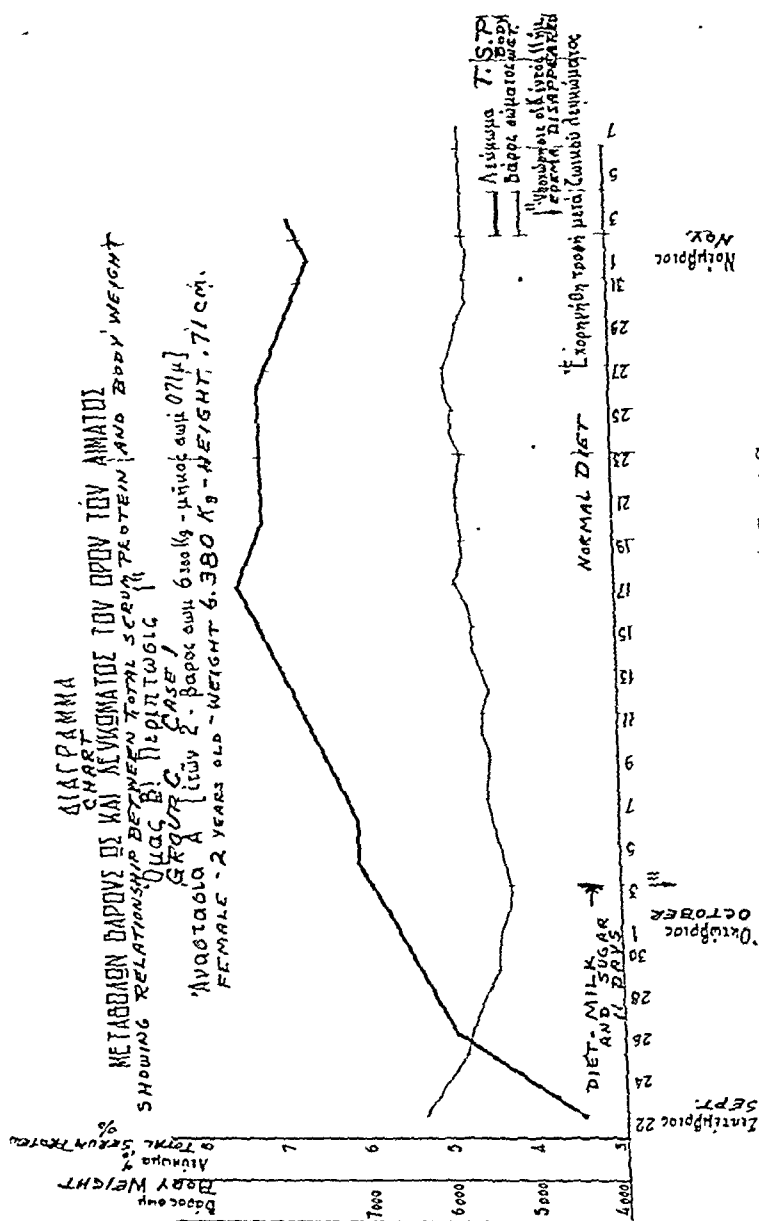


Chart V.—Illustrating Case 1, Group C.

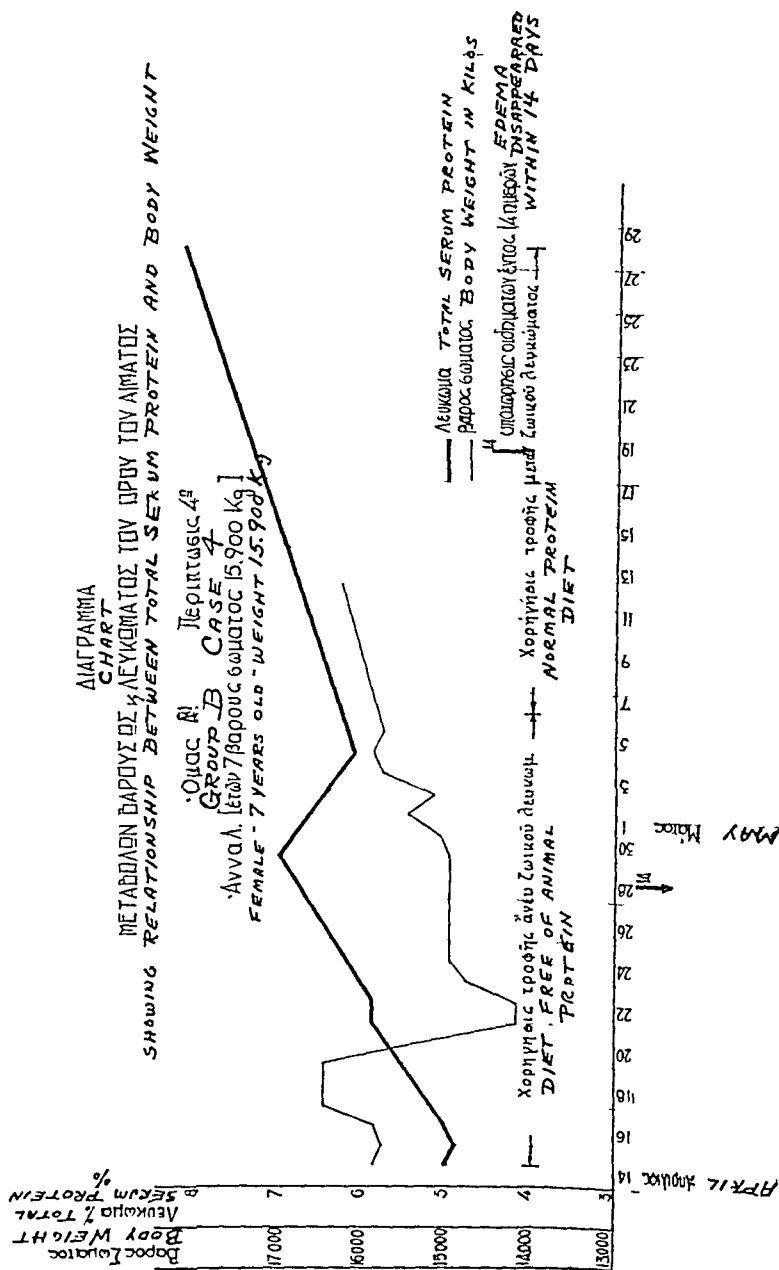


Chart IV.—Illustrating Case 4, Group B.

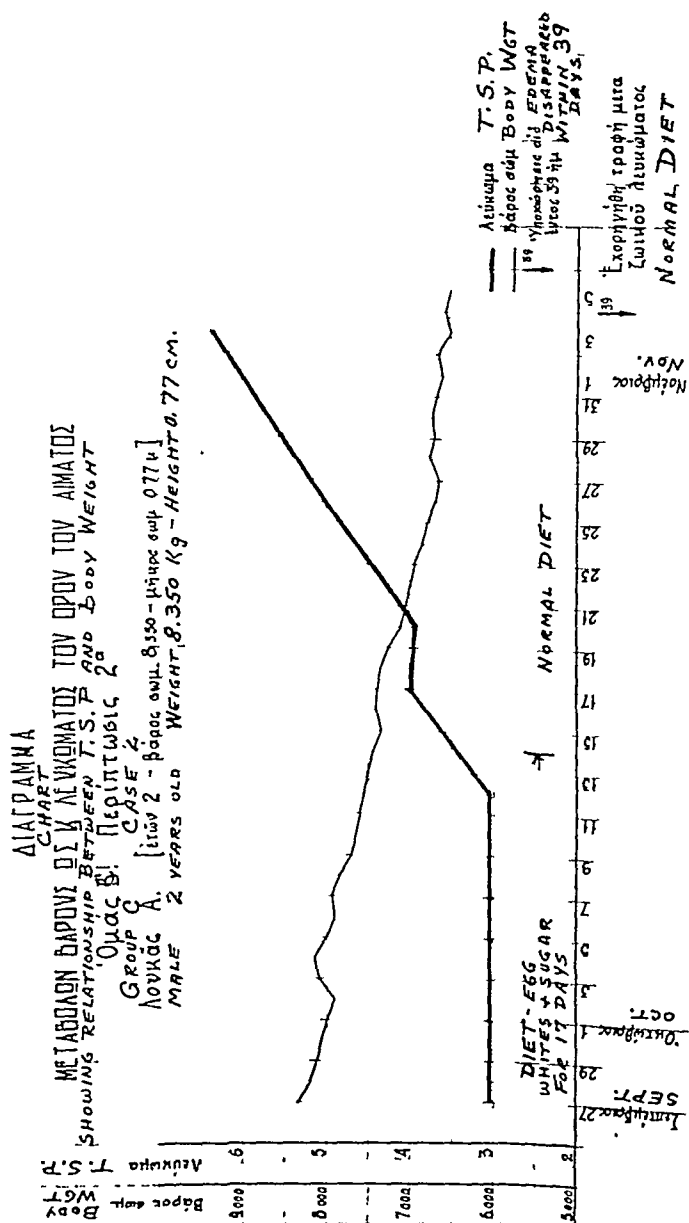


Chart VI.—Illustrating Case 2, Group C.

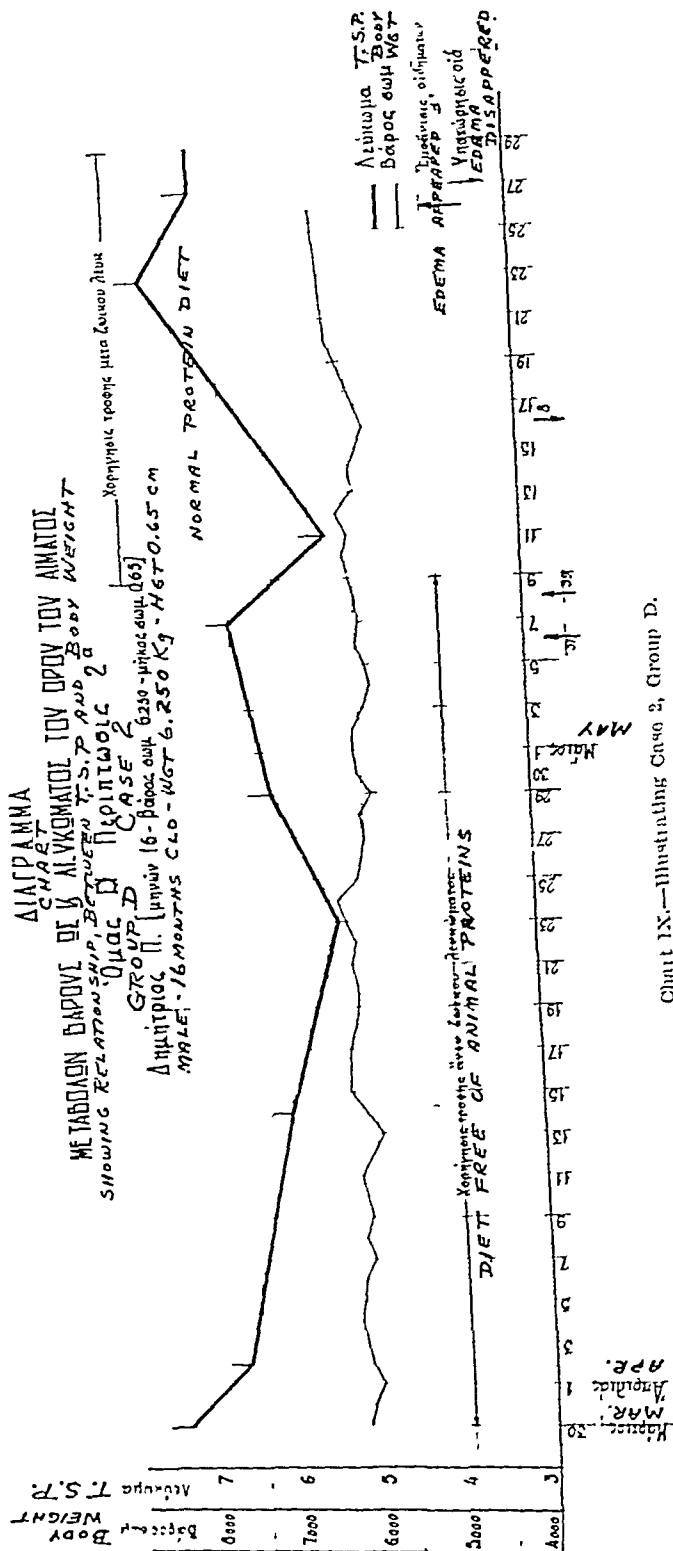


Chart IX.—Illustrating Case 2, Group D.

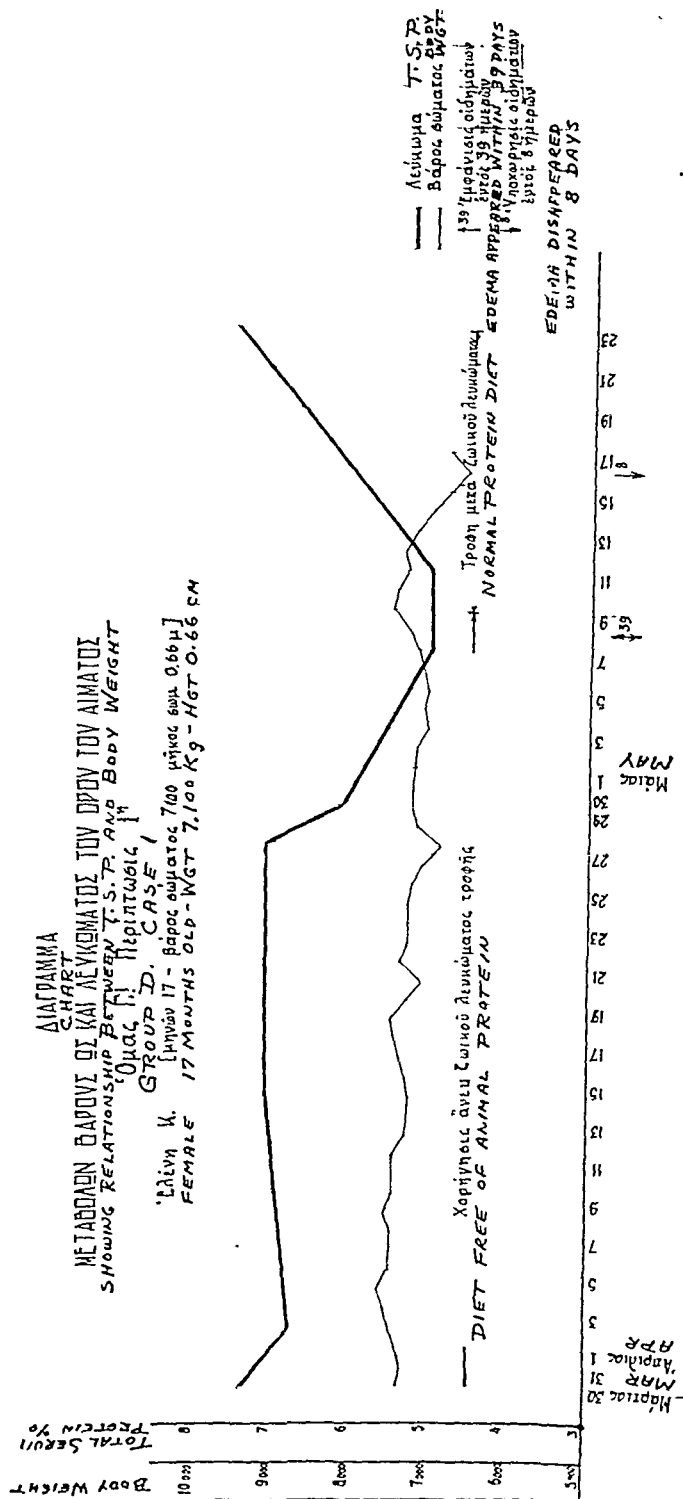


Chart VIII.—Illustrating Case 1, Group D.

Group D.—In these three children who received small amounts of vegetable protein and no animal protein, we found at the onset of the observations normal TSP values, namely 7.42 Gm. per 100 c.c. in the first and second cases and 8.49 Gm. per 100 c.c. in the third. The daily food intake contained a sufficient number of calories. The protein content was inadequate in opposition to fat, which was more than adequate. The carbohydrate content was slightly below normal values. In addition, vitamin B complex was given parenterally. During the progress of the observations our repeated serum protein determinations revealed a continuous drop in the serum protein level. Values below normal were encountered in the first patient on the thirty-eighth day (5.03 Gm.), in the second on the twenty-fourth day (5.26 Gm.), and in the third on the twentieth day (5.03 Gm. per 100 c.c.). During this period there was a fall in body weight. A few days before the appearance of edema the weight increased. Concomitantly with the above phenomena there appeared insidiously increasing weakness, pallor, emaciation, diminution of subcutaneous adipose tissue, polyuria, bradycardia, and arterial hypotension. During the thirty-ninth day in the first patient, the thirty-seventh in the second, and the twentieth in the third, there appeared dependant edema over the lower extremities. This became more marked during the supervening two days in the first two patients. In the third the edema disappeared on the tenth day and re-appeared again on the thirty-ninth day to become more pronounced during the superseding two days. On the average the hypoproteinemia appeared on the twenty-seventh to thirty-eighth day while the appearance of edema occurred on the thirty-second day after the withdrawal of animal protein from the food. From the fortieth day on in the first two patients and the forty-first day in the third, we interrupted the above regimen and administered animal protein. A few days later we observed an increase in TSP and the body weight decreased while the edema diminished. This latter disappeared seven days later in the first two children and six days later in the third. At this point the serum proteins value were of normal value.

CONCLUSIONS

1. The nutritional edema is due to hypoproteinemia and the resulting low osmotic value, which in turn results in the exit of water from the blood to the tissues.
2. There is a direct relationship between the degree of hypoproteinemia and edema.
3. In the younger children there is an absolute necessity for animal protein, while in older age groups large amounts of vegetable protein, ranging from two to threefold the normal values, may induce a temporary improvement.
4. Egg white alone was demonstrated to have no effect on hypoproteinemia and nutritional edema in opposition to milk and egg yolk.
5. Other factors such as changes in capillary permeability, lack of fat, avitaminosis, excessive salt and water intake, have only a contributory significance.
6. The susceptibility to nutritional edema is more marked in the case of boys as opposed to girls.

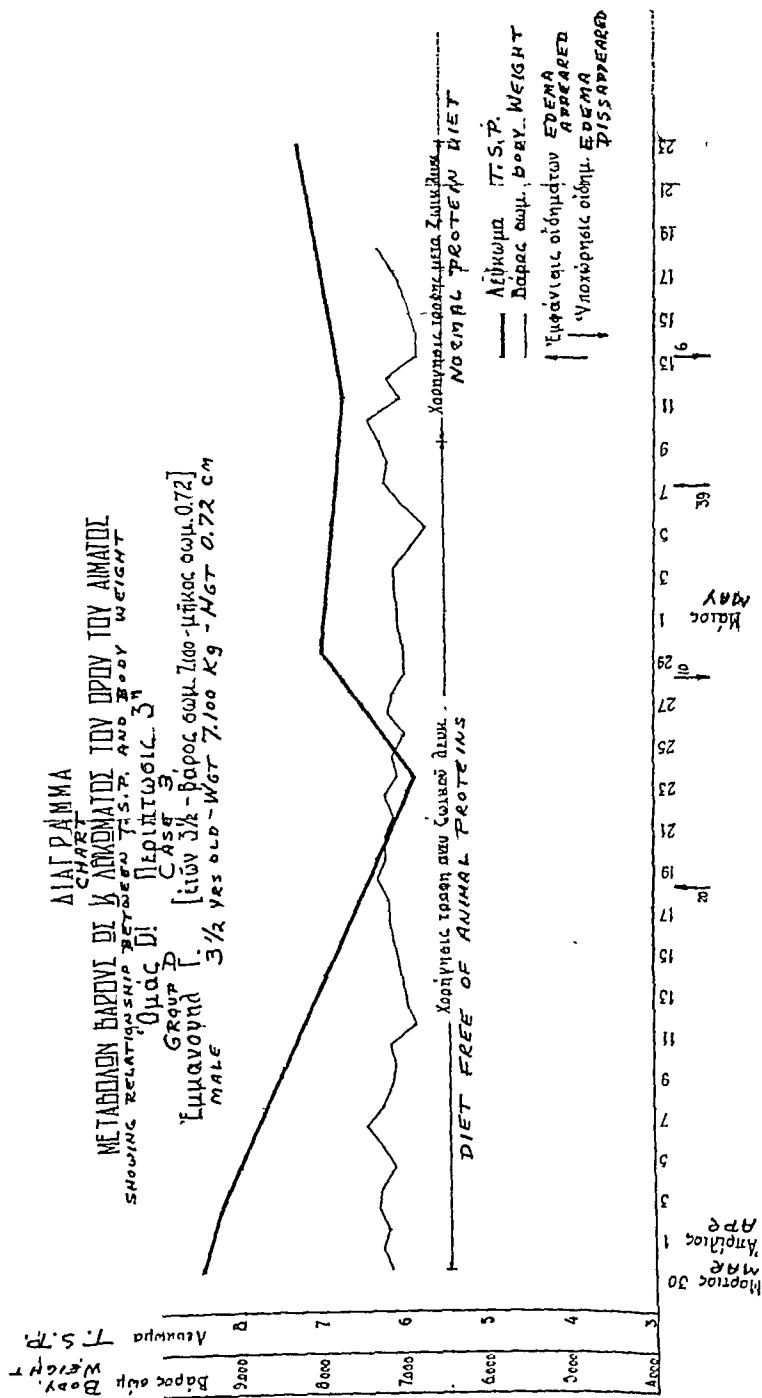


Chart X.--Illustrating Case 3, Group D.

SUBLINGUAL METHYL TESTOSTERONE FOR BOYHOOD EMOTIONAL, PHYSICAL, AND GENITAL IMMATURITY

FLOYD E. HARDING, M.D.
LOS ANGELES, CALIF.

METHYL testosterone enlarges all parts of the male genitalia before or during puberty. It increases the size of the testicle to some extent although there is greater growth in the penis, scrotum, vas deferens, and prostate. When small doses of it are given, however, it does not initiate the onset of puberty in a child too young for this occurrence.

In boys with unusually small genitalia, a neurosis may be caused by the fear of abnormality and by the cruelty of other children who make disparaging remarks. This condition is easily cured with methyl testosterone without apparent harm.

Observation of the marked benefit obtained in the treatment of neurosis due to undersized genitalia prompted the trial of methyl testosterone for patients of a similar type with poor muscular development and an emotional response like that of a younger child. After a good initial result in a few patients, it seemed desirable to give a group of immature boys methyl testosterone to note its general effect. Other clinicians have reported benefit with this type of treatment.^{1-3, 11, 13-14} Publications have also shown that this androgen increases the rate of growth in short individuals,^{2, 3} and that the creatine excretion is increased.⁴ There is said to have been improvement in the muscular performance of older men.¹²

Extensive oral use of steroid substances in the female has given information on the variation in absorption and effect of these preparations and has helped in evaluating the response with methyl testosterone when given to boys.⁵⁻¹⁰

METHOD OF TREATMENT

The sublingual method of administration was chosen because the hormone was said to be a little more effective when used in this manner instead of being swallowed.¹⁶ The tablets of methyl testosterone* were held under the tongue or between the teeth and the cheek and allowed to dissolve slowly to obtain as much local absorption as possible. They each contained 5.0 mg. of material and were cut in half or in fourths for the 2.5 mg. or 1.2 mg. doses. The total daily dose given each patient is found in Table I.

Treatment was given continuously up to two months, after which, if further development was required, the medication was discontinued for one month, then given another two months. This precaution, although probably unnecessary with the small doses used, was taken in order not to upset other glandular function over too long a period.

From the Department of Endocrinology, Ross-Loos Medical Group, Los Angeles, Calif.
*The Metadren Linguts (methyl testosterone) were obtained from Ciba Pharmaceutical Products, Inc., Summit, N. J.

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TABLE I. CLINICAL MATERIAL AND THE DOSAGE OF METHYL TESTOSTERONE

CASE NO.	AGE	HEIGHT (INCHES)	WEIGHT (LB.)	BODY TYPE	PENIS COVERED	SIZE OF GENITALIA	PHYSICALLY WEAK	EMOTIONALLY IMMATURE	MISC.	REDUCING DIET	(MG.) DOSE DAILY	MONTHS OF TREATMENT
1	11	63.0	120	O	Pc	G	—	I	—	D	2.5	2.0
2	2	33.0	30	O	Pc	G	—	—	—	—	1.2	2.4
3	10	52.5	66	N	—	G	W	—	S	—	2.5	4.0
4	13	62.0	158	O	C	V	—	I	—	D	10.0	2.9
5	14	57.7	101	O	—	G	—	—	S	—	2.5	20.0
6	13	61.5	125	O	Pc	G	—	I	—	—	5.0	2.0
7	12	64.0	173	O	—	V	W	I, F	—	D	5.0	2.7
8	7	46.0	43	N	—	V	—	I, F	S, E	—	2.5	4.0
9	13	62.5	126	O	C	V	W	—	—	D	5.0	6.0
10	11	62.0	120	O	Pc	G	W	—	—	D	5.0	3.0
11	11	59.7	107	O	—	G	—	I, F	M	—	5.0	6.6
12	12	63.5	150	O	C	V	—	I	—	D	5.0	6.0
13	9	53.0	108	O	—	V	—	I	M	D	5.0	3.2
14	9	54.2	77	O	—	G	W	I, F	Cr	—	2.5	6.0
15	11	56.0	105	O	—	G	W	I, F	—	D	5.0	1.4
16	1	29.0	25	O	C	V	—	—	—	D	.6	1.8
17	12	60.0	124	O	Pc	G	—	I	—	D	5.0	2.3
18	16	61.7	96	U	—	V	—	—	S	—	5.0	8.0
19	12	65.2	185	O	C	V	—	—	Ga	D	5.0	13.0
20	11	54.0	58	U	—	V	—	—	S	—	10.0	5.0
21	12	60.5	122	O	Pc	G	W	—	—	D	5.0	2.0
22	8	54.6	104	O	C	V	—	I	—	D	5.0	6.5
23	12	59.0	106	O	C	V	W	—	—	—	5.0	3.0
24	15	63.0	106	N	—	G	—	I	—	—	5.0	6.0
25	9	59.2	134	O	Pc	G	—	—	Cr	D	5.0	1.8
26	1	29.5	25	O	C	V	—	—	—	—	1.2	3.7
27	13	64.7	130	O	—	G	—	I, F	Cr	D	5.0	7.0
28	10	52.5	91	O	—	G	—	—	S	D	2.5	6.0
29	12	58.5	84	N	—	V	—	I, F	—	—	5.0	8.1
30	9	57.0	117	O	C	V	W	—	—	D	5.0	4.8
31	1	28.0	24	O	C	V	—	—	—	D	2.5	2.3
32	10	56.7	81	N	—	G	—	I, F	E	—	2.5	3.0
33	12	62.5	105	O	Pc	V	W	I, F	—	—	5.0	1.4
34	10	54.0	105	O	Pc	G	W	I, F	—	D	1.2	5.2
35	10	56.0	93	O	Pc	V	—	I, F	—	D	10.0	3.2
36	9	53.0	64	N	—	G	—	—	M	—	5.0	2.2
37	8	52.7	77	O	—	G	—	I, F	—	D	2.5	4.0
38	11	56.7	87	O	—	G	W	I	—	D	5.0	5.0
39	11	61.0	114	O	Pc	G	—	—	Cr	D	5.0	5.0
40	11	61.0	118	O	Pc	G	—	—	E	D	2.5	2.4
41	11	62.5	106	O	—	G	—	—	Gy	D	5.0	2.1
42	11	59.0	98	O	C	V	W	I, F	Gy	D	5.0	3.9
43	14	56.7	80	N	—	G	W	I	S	—	5.0	6.8
44	13	58.5	86	N	—	G	—	—	S	—	5.0	2.8
45	14	64.5	128	O	—	G	W	I	Gy	D	5.0	4.0
46	13	61.2	126	O	C	V	—	I	—	D	5.0	1.4
47	7	52.0	84	O	—	V	—	—	Cr	D	2.5	2.8
48	10	51.2	59	N	—	G	W	—	S	—	2.5	2.0
49	10	57.5	104	O	Pc	G	—	I	—	D	5.0	2.7
50	8	54.5	73	N	—	G	W	I, F	E	—	1.2	9.3
51	12	56.0	74	N	—	G	W	—	S	—	2.5	4.5
52	12	59.0	107	O	Pc	G	W	F	—	D	5.0	2.0
53	14	61.5	110	O	Pc	V	—	I	S, Gy	D	5.0	9.9
54	15	69.2	178	O	Pc	G	W	I	E	D	5.0	2.2
55	11	58.5	113	O	Pc	G	W	—	E	D	5.0	1.2
56	13	61.5	160	O	C	V	—	—	Gy	D	5.0	4.0
57	9	58.0	105	O	C	V	W	I, F	—	D	10.0	9.0
58	13	63.0	91	U	—	G	W	I	—	—	2.5	2.0

O, obese; N, normal weight; U, underweight; C, penis covered by fat mounds; Pc, penis mature; covered by fat mounds; S, too short; E, enuresis; Gy, gynecomastia; I, emotionally immature; acts like younger child; W, physically weak; poor muscular development; F, poor average; V, genitalia very small; Cr, cryptorchidism; D, reducing diet; G, genitalia smaller than (mm).

The obese patients were given a low-calorie vitamin-rich diet made up largely of fruits and vegetables but containing sufficient protein for a growing child. The underweight children were given a high-calorie vitamin-rich diet.

CLINICAL MATERIAL

All of the patients treated had small genitalia. The penis and testes were small, and the scrotum was also underdeveloped. The fat mons frequently covered the penis, causing urination to be difficult and embarrassing. There were cases of pseudo- and true cryptorchidism. All of the children and their parents believed that the condition was abnormal and that improvement in size was desirable if it could be obtained. Several of the children had a neurosis wholly or partly due to the cruelty of other children laughing or making remarks about the infantile nature of their organs. Many boys were emotionally immature or physically weak. Some complained of enuresis. Failure in school or very poor work in spite of good intelligence was often reported. At times growth was a problem, as the height age was less than the chronological age. It was believed that the small size of the genitalia on examination was usually insufficient reason for therapy, unless some other physical or psychological abnormality existed; and in most children treated two or three indications were found to be present. Further details can be found in Table I.

RESULTS

Genital development was considered satisfactory in all patients taking methyl testosterone. The penis increased in size more rapidly than the testicles but the latter became definitely larger also. There was no evidence of testicular atrophy. These glands were of normal shape and firmness after treatment. The medication was discontinued when the penis became large enough to be considered within the limits of normal and about average size for the height and general development of the child. No attempt was made to enlarge the penis beyond what was considered normal. In the obese patient, reducing the size of the fat mons and enlarging the penis greatly improved the physical appearance and facilitated urination and cleanliness. The scrotum became more pendulous and rugose. There was an increase in length of the ductus deferens and some development of the prostate. The testicles stayed down better in the pseudo-cryptorchid patients and in four boys with true cryptorchidism a cure was effected. One boy with cryptorchidism and inguinal hernia had an operation. Three of the older boys began to have nocturnal emissions. Those going through puberty had an increase in the amount of pubic hair. In the younger children there was no growth of pubic hair. There was great variation in the rapidity of development. Some boys developed in two to three months with very small doses of methyl testosterone, whereas other boys developed slowly with larger doses. In general the very short children or those with very small testicles required longer treatment.

Methyl testosterone definitely increased the rate of growth. During treatment and in the months immediately following medication the entire group of fifty-eight children averaged 3.2 inches growth per year per individual. Sixteen

DISCUSSION

Taking everything into consideration the results were quite satisfactory and often impressive.

A note of warning is due here. It is not intended to imply that methyl testosterone is a cure for psychoneurosis, weakness, or underweight. The only neurosis cured by its administration was the one due to embarrassment caused by the small genitalia, although the children frequently became less emotionally immature. All patients showed enlargement of the penis, but only part of the patients in this carefully selected group had improvement in weight, muscular development, and growth greater than would be expected without treatment.

It must be kept in mind that most cases of cryptorchidism, cases of abnormality of the genitalia other than smallness of size, and most other endocrine disorders were not included in the series treated with methyl testosterone. Some boys age 16 to 21 were seen whose genitalia did not improve to the extent of being within the range of normal size. Older children diagnosed as eunuchoids were not included in the group reported here; those treated usually responded more slowly and required larger daily doses than the boys in this group. In adults, the most effective form of substitution therapy was found to be the implantation of testosterone pellets, although other methods were satisfactory.⁵

Anterior pituitary-like substance appears to be better than methyl testosterone for the treatment of cryptorchidism.⁶ However, the two are sometimes combined where there is marked underdevelopment. If anterior pituitary-like substance is used instead of methyl testosterone, there is greater growth of the testicle and less enlargement of the penis. After the testicle increases in size, it produces more testosterone, which in turn causes some growth of the other parts of the male genitalia.

It is frequently argued that treatment is unnecessary as the genitalia become normal with puberty and all one need do is to wait. This reasoning is superficial as it does not consider the possibility that the handicapped child may develop into a neurotic adult or a poor citizen. The physical or emotional immaturity results in poor play and school work. The child grows up into an adult having failed to learn how to get along satisfactorily with other people. Since enuresis also may be due to physical and emotional immaturity, treatment with methyl testosterone at an early age may cure those boys who would improve spontaneously years later at puberty.

How the adult size of the genitalia of the fifty-eight patients treated would compare with the adult size of a similar group used as a control is unknown at the present time.

Testosterone propionate is believed to inhibit spermatogenesis temporarily in adults.¹² However, before puberty there is a physiologic lack of spermatozoa formation. None of the boys in this group had had any semen at the time treatment was instigated. Also, the dosage used was much smaller than that required for inhibition of spermatogenesis.

Although small doses of methyl testosterone increase the size of the penis and testicles in the child, a dosage of 20 mg. daily has no effect on the size of these organs in the normal adult. Some improvement is obtained in the size

controls, ages 8 to 15 years, of essentially the same endocrine types, were not given methyl testosterone and they grew on an average of 2.3 inches per year. The average boy from 8 to 14 years of age grows 2.2 inches per year. The eleven short boys receiving methyl testosterone grew 3.3 inches per year on an average. This was faster than they grew in the year prior to taking methyl testosterone according to their own statements, although exact measurements were not available. Their appearance was good after treatment as growth was proportionate.

Physical improvement was frequently outstanding, especially in the weak, flabby, obese boy who was often somewhat effeminate, and in the thin child with little muscular development and stamina. The shoulders broadened, the muscles in the neck, back, and shoulders becoming definitely larger. The greater shoulder breadth made the relation between shoulders and pelvis more like that of the adult man. There was also some improvement in other skeletal muscles; more work could be done without tiring; physical tasks were performed with greater speed and facility. The boys played better, because now they occasionally won games; they frequently gave up playing with younger children. The feet and hands became larger. There was usually some gain in weight except when the patient was following a reducing diet. Quite naturally, this increase in pounds was more striking in the thin individual.

Other noticeable improvements showed in the lessening of the feeling of inferiority and of the exhibition of emotional immaturity; the children cooperated better with parents and teachers and took more responsibility. They were less inclined to act like younger children and became more amenable to reason, showing an improvement in their personalities. To some extent they seemed to mature psychologically and became more dependable, causing their actions to be more predictable. The children in this group were normal mentally, yet failure at school was common. The school work improved with lessening in nervousness and restlessness, while there was an upward trend in concentration and attitude. Bad childhood habits were more easily broken; enuresis was cured in two and improved in two of the six patients who had not broken this tendency.

Most of the children were observed for from one to four years following completion of treatment. They continued to develop normally. A few were given another course or two of treatment. They did well when compared with nontreated patients previously observed. Epiphyseal closure came at the expected time.

UNDESIRABLE EFFECTS

No bad effects were noticed except for sexual stimulation in three patients who had the masturbation habit. These boys knew beforehand that the tablets might cause more frequent erections. Treatment was stopped and later resumed with smaller doses. The others had no knowledge of the physiologic effects of the tablets and were untroubled with the small doses given. The tablets caused some of the boys to have acne of a minor nature.

No allergy or idiosyncrasy was encountered. It was observed that methyl testosterone was well tolerated by the gastrointestinal tract.

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Although small doses of methyl testosterone increase the size of the penis and testicles in the child, a dosage of 20 mg. daily has no effect on the size of these organs in the normal adult. Some improvement is obtained in the size

of the atrophic penis, accessory genitalia, and secondary sex characteristics if treatment is begun after atrophy of the testicles from mumps, injury, hernia operation, infection, or irradiation, or after castration.

CONCLUSIONS

Methyl testosterone was administered in small daily doses to a carefully selected group of fifty-eight children, mainly between the ages of 7 and 15 years. The sublingual method was used.

Satisfactory development of primary and secondary sex characteristics occurred. In some patients there was an increase in weight and production of greater muscular strength. The average rate of growth as determined by height was increased to 3.2 inches per year. The neuroses due to the presence of very small genitalia were cured. There was less emotional immaturity.

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CEREBRAL COMPLICATIONS IN PERTUSSIS

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INTRODUCTION

PERTUSSIS is still a challenge to the medical profession, especially when it occurs in infants under one year of age. Of all the infectious diseases none is more important from the point of view of morbidity and mortality. The disease is most serious when complicated by pulmonary or cerebral manifestations.

Over 200,000 cases of whooping cough are reported annually in the United States, with 5,000 to 7,000 deaths. The high incidence among infants under one year, and the high mortality rate in this group are especially striking. The late sequelae in this disease have been infrequently described in the literature, although they occur in a large number of the patients.

A great variety of cerebral complications in pertussis have been described. Clinical findings have included convulsions, monoplegia, hemiplegia, diplegia, paraplegia, deafness, blindness, aphasia and idiocy. Pathologically, meningeal and cerebral hemorrhages, meningitis, encephalitis, and thrombosis of cerebral veins and cerebral sinuses have been observed. Reports of some of these complications or sequelae have been frequently published; others, because of their rare occurrence, have been infrequently mentioned in the literature.

The purpose of this paper is to present an analysis of forty-seven cases of clinical cerebral complications which occurred in 6,002 patients with pertussis admitted to the Kingston Avenue Hospital for Communicable Diseases from 1932 to 1946 inclusive.

INCIDENCE

The incidence of cerebral complications in pertussis cannot be definitely established since not all patients with pertussis in a community are hospitalized. A review of the literature would also make it impossible to attempt such an estimate. For example, Valentine¹ reviewed the records of eighty-three cases of pertussis reported between the years 1880 and 1900 and found that sixty-four of the patients had convulsions during their illness. Of these sixty-four patients, fourteen died, twenty-two developed spastic paralysis, and twenty-eight showed residual neurological disturbances—a very high incidence as compared to the experiences of others.

Bazan and Maggi² reported fifteen cases of encephalitis in 600 cases of pertussis observed during a five-year period, an incidence of 2.5 per cent. Most of these cases of encephalitis occurred in the first two years of life. Vor dem Esche³ reported 1,115 patients with pertussis seen during a two-year period.

From the Kingston Avenue Hospital for Communicable Diseases, Brooklyn.

TABLE I. INCIDENCE OF CEREBRAL COMPLICATIONS IN PERTUSSIS AND PERCENTAGE MORTALITY AS REPORTED BY VARIOUS OBSERVERS

AUTHOR	YEAR	NO. CASES PERTUSSIS	NO. CASES WITH CEREBRAL COMPLI- CATIONS	NO. DEATHS FROM CEREBRAL COMPLI- CATIONS	PER CENT MORTAL- ITY
1. Valentine, P.	1890	83	64	14	22
2. Husler, J., and Spatz, H.	1924	?	?	?	72
3. von dem Esche, C.	1931	1,115	172	103	60
4. Ley, R. A., and Dagnelie, J.	1932	135	8	7	86
5. Grenet, H., and Mourrut, E.	1933	238	22	20	87
6. Ellison, J. B.	1934	?	72	46	63
7. Habel, K., and Lucchesi, P.	1938	516	41	32	78
8. Bazan, F., and Maggi, R.	1940	600	15	12	80
9. Litvak, A. M., et al.	1932- 1946	6,002	47	19	40

Of these, 172 showed cerebral symptoms, an incidence of 14 per cent. (See Table I.)

Hospital admissions of pertussis patients represent but a small percentage of the total number of cases and comprise the seriously ill and those with inadequate facilities for home care. On the other hand, convulsions in the course of pertussis may indicate the onset of complications such as bronchopneumonia, otitis media, tuberculosis, tetany, alkalosis, apnea, spasm of the glottis with anoxemia, and pneumothorax. Considerable care was exercised in this study to eliminate the patients with transient convulsive seizures which might have been due to the complications just mentioned. Thus, of a total of 6,002 hospitalized patients with pertussis at the Kingston Avenue Hospital, there were forty-seven patients with cerebral complications in a fifteen-year period, an incidence of 0.8 per cent. There were no significant dramatic variations from year to year in the number of cerebral complications. The general mortality rate from 1932 to 1938 inclusive was 9.4 per cent (Table II), while the general mortality rate from 1939 to 1946 was 3.3 per cent (Table III). This dramatic drop in the mortality rate was due to the use of sulfa drugs, hyperimmune human serum, and penicillin. The mortality rate in patients with cerebral complications of pertussis, however, has not been materially changed by these therapeutic agents.

TABLE II. ANALYSIS OF PERTUSSIS PATIENTS ADMITTED TO THE KINGSTON AVENUE HOSPITAL FROM 1932 TO 1938 INCLUSIVE

YEAR	PERTUSSIS PATIENTS	NO. DEATHS	PER CENT MORTALITY	PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS	NO. DEATHS
1932	403	45	11.2	1	0
1933	336	48	14.3	3	1
1934	430	32	7.4	1	1
1935	493	56	11.4	2	1
1936	229	17	7.4	8	2
1937	217	14	6.4	6	0
1938	650	49	7.7	3	1
Total	2,758	261	9.4	24	6

TABLE III. ANALYSIS OF PERTUSSIS PATIENTS ADMITTED TO THE KINGSTON AVENUE HOSPITAL FROM 1939 TO 1946 INCLUSIVE

YEAR	PERTUSSIS PATIENTS	NO. DEATHS	PER CENT MORTALITY	PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS	NO. DEATHS
1939	293	9	3.1	7	3
1940	346	16	4.0	6	4
1941	487	9	3.9	3	1
1942	645	22	3.4	1	1
1943	452	13	2.9	2	1
1944	285	12	4.2	2	2
1945	505	13	2.6	1	0
1946	231	5	2.1	1	1
Total	3,244	109	3.3	23	13

In this country about 200,000 cases of pertussis occur each year, with an average mortality rate of 3 per cent. When the disease is complicated by cerebral symptoms, the mortality rate rises abruptly. For example, the death rate in the series reported by Valentine¹ was 22 per cent. Husler and Spatz⁴ reported a mortality rate of 72 per cent; Grenet and Mourrut⁵ reported twenty-four cases complicated by convulsions, with a mortality rate of 87.5 per cent; von dem Esche³ reported a mortality rate of 60 per cent in 172 cases; Habel and Lucchesi⁶ reported forty-one cases and found that the general mortality rate of 5 or 10 per cent for all hospitalized patients with pertussis uncomplicated by convulsions rose to 60 per cent when convulsions complicated the disease. Ley and Dagnelie⁷ reported a mortality rate of 86 per cent. The average mortality rate for whooping cough in our series of 6,002 cases was 6.1 per cent. However, in the presence of cerebral complications, the mortality rate rose to 40.4 per cent.

LABORATORY DATA

Spinal fluid studies were done in thirty-eight of the forty-seven patients, and the fluid was found to be clear in every instance. The sugar content was normal except for two recordings of 166 and 160 mg. per cent. All fluids were sterile on culture and no organisms were seen in smears. Only seven of the specimens examined had a cell count over fifteen, the highest being 100 per cubic centimeter. The cells were almost always of the lymphocytic variety. There was no parallelism between the pleocytosis and the increase in the protein level, which varied from 18 to 120 mg. per 100 c.c. There was no correlation between the cell count of the spinal fluid, the severity of the complication, and the outcome in the individual patient.

The white blood cell count varied from 8,250 to 68,000 with the percentage of lymphocytes varying from 42 to 87 per cent. Similarly, there was no correlation between the severity of the complication, the prognosis of the individual case, and the total white count.

TEMPERATURE

The onset of cerebral complications in pertussis was almost always accompanied by a rise in the temperature. All but seven of the patients had an elevation of temperature ranging from 100 to 105° F.

SEX

It has been pointed out by other observers that the incidence of cerebral complications in pertussis is higher in female than in male patients. Our studies substantiated these observations. Of the forty-seven patients with pertussis associated with cerebral complications, twenty-seven were female and twenty male. The fatality rate was nearly equally divided between male and female patients. We have no explanation to offer for the higher incidence of cerebral complications in female subjects. However, von dem Esche,³ in his series of 172 cases, found the sexes to be equally divided. Cruickshank⁸ also remarked about the greater incidence of cerebral complications among female patients.

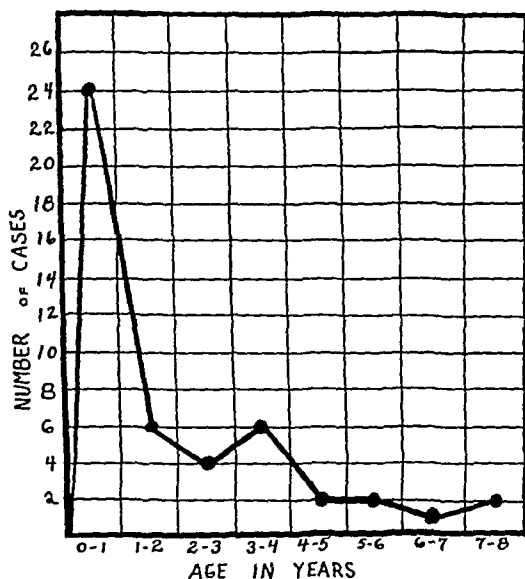


Chart I. Age incidence of cerebral complications in pertussis (47 cases).

AGE

It should be noted that in our series 50 per cent of the patients who developed cerebral complications were under one year of age, 60 per cent under 2 years (Chart I). Of forty-one patients reported by Habel and Lucchesi,⁶ 75 per cent were under the age of one year. Zischinsky,⁹ in a report of 12,577 cases of pertussis, found 83 per cent to be in infants 2 years of age and under, but unfortunately says nothing about the incidence of cerebral complications in this group.

Over a ten-year period from 1937 to 1946 inclusive, 4,111 patients with pertussis were admitted to the Kingston Avenue Hospital. Of these, 172 died. Of the total number of patients, 1,406 were infants under one year of age. One hundred twenty-six of these died. In other words, 73 per cent of the deaths that occurred during this ten-year period occurred in infants under one year of age. (Table IV.)

TABLE IV. ANALYSIS OF PERTUSSIS CASES AND DEATHS WITH PARTICULAR REFERENCE TO INFANTS UNDER ONE YEAR OF AGE

	YEAR										TOTAL
	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	
Total number patients	217	650	293	346	487	645	452	285	505	231	4,111
Total number infants under one year	43	202	99	101	134	263	158	124	178	104	1,406
Total number deaths	14	49	9	16	19	22	13	12	13	5	172
Total number deaths under one year	7	33	8	14	13	18	6	11	12	4	126

ONSET OF SYMPTOMS

Nelson¹⁰ stated that cerebral complications in pertussis seldom appear during the catarrhal stage or even during the early part of the paroxysmal stage. He found that cerebral complications usually made their appearance at the peak of the paroxysmal stage and occasionally after it had begun to subside.

In our series it was noted that the onset of cerebral complications occurred during the third and fourth weeks of the disease in 72.5 per cent of the cases, while in the remaining 27.5 per cent the onset occurred in the first, second, fifth, and sixth weeks (Table V).

TABLE V. ONSET OF CEREBRAL COMPLICATIONS IN PERTUSSIS WITH REFERENCE TO STAGE OF THE DISEASE

STAGE OF DISEASE	NO. CASES
1st week	2
2nd week	6
3rd week	18
4th week	13
5th week	7
6th week	1
Total	47

ETIOLOGY

Numerous theories have been advanced regarding the etiology of cerebral complications in pertussis. Among the most recently advanced theories are those enumerated by Ellison:¹¹

1. *Hemorrhage*.—This theory assumes that the nervous manifestations are due to gross mechanical interference with the circulation of blood in the brain due to the violence of the cough. The early authors such as Rhein,¹² Loschner,¹³ and Smith¹⁴ considered hemorrhages as the causative factor. West¹⁵ and Luce¹⁶ have reported cases in which, at autopsy, were found minute hemorrhages, edema, and cellular degeneration in the brain. Hockinjos¹⁷ reported forty-two patients with post-mortem findings in some cases. The chief findings were minute hemorrhages in various parts of the brain, but he felt these to be insufficient to account for the outcome. Hockenbach¹⁸ reported twenty-three cases in which a clinical diagnosis of brain hemorrhage had been made. There were nine post-mortem examinations of which five showed hemorrhages into the gray matter, two showed hemorrhages into the cortex, and two showed hemorrhages between the pons and dura. Cannelli¹⁹ reported two deaths and suggested that minute hemorrhages had occurred either as a result of the action

of carbon dioxide on the vessels during the asphyxia due to a paroxysm or because of increased intraventricular pressure. Gross hemorrhages have been reported by Cabot.²⁰

Ford²¹ stated that until recent years it was customary to attribute the cerebral symptoms to hemorrhages, but many observers have noted that hemorrhages are sometimes absent or when present are not always extensive enough to explain the symptoms. He does not believe that hemorrhages alone, gross or microscopic, are responsible for the various cerebral complications.

Litvak²² reviewed the reports of seventeen cases of pertussis in which visual disturbances occurred. He attributed these in some cases to hemorrhages into the internal capsule, and in others to retrobulbar neuritis.

2. *Spasmophilia*.—Powers²³ report of five patients suffering from rickets and pertussis gave fresh impetus to this theory. His work was subsequently repeated by others. Askin and Zimmerman²⁴ and Litvak²² reported normal calcium-phosphorus relationships in their patients, and Regan and Tolstouhoy²⁵ reported normal calcium levels on fifty-eight patients. However, the blood phosphorus was consistently below normal in 211 determinations. Trambusti and Sertori²⁶ did serum calcium determinations in eleven uncomplicated cases and found an average value of 8 mg. per 100 c.c. in the early stages of the disease. One 5½-month-old baby with clinical signs of tetany had a calcium level of 2.4 mg., but no convulsions were observed. The only other author to report convulsions due to low calcium levels was Bluhdorn.²⁷

3. *Meningoencephalitis*.—This theory postulates the action of some biologic agent on the central nervous system, or the action of a toxin released in the respiratory tract by the Bordet-Gengou bacillus which may produce inflammatory changes in the brain. Criticism of this theory is based chiefly upon the lack of consistency in the pathologic changes and the fact that no biologic agent or toxin has been identified. However, many authors report their cases as "encephalitis," such as Askin and Zimmerman,²⁴ who base their opinions on the finding of diffuse scattered focal collections of small, deeply staining mononuclear cells, and occasional mononuclear cells with large, pale, vesicular nuclei and abundant cytoplasm present in these cellular foci. Singer²⁸ reported six cases in which there was a diffuse "hemorrhagic encephalitis," and he differentiates whooping cough encephalitis from other forms of encephalitis by the marked tendency toward diffuse microscopic hemorrhages. Hada²⁹ reported a patient with acute encephalitic changes in parts of the brain adjacent to a profuse exudate in the sulci. Husler and Spatz⁴ demonstrated irreversible degenerative changes in the cortex, dentate nucleus, and corpus striatum without hemorrhage in two patients dying of pertussis complicated by convulsions. They describe a typical regressive change in the nerve cells of the cortex with loss of the staining properties of the cell except the nucleus. This suggested to them an encephalitic basis for the disease. Neuberger³⁰ described similar lesions in two patients but suggested that the changes were due to ischemic necrosis resulting from air emboli. Joehims³¹ reported similar findings in a case and suggested the term "whooping cough encephalopathy." Strauss,

Rabiner, and Ginsburg³² place whooping cough encephalitis in the class of demyelinating diseases of unknown origin, together with measles, smallpox, mumps, and other varieties of encephalitis.

4. *Neurotoxin*.—This theory assumes the presence of a toxin with a specific action on the central nervous system. The principal criticism directed against this theory is that the Bordet-Gengou bacillus does not produce an exotoxin. Mikulowski³³ also advanced the theory that the blood contained a toxin capable of affecting the tissues of the central nervous system and the endothelial lining of the vessels of the brain.

5. *Angiospasm*.—This theory, first advocated by Spielmeyer (cited by Ellison³¹), assumes the presence of a reflex mechanism due to functional disturbances of the circulation caused by repeated violent alterations in pressure produced by spasms of coughing. Canelli¹⁹ reported two deaths and suggested that minute hemorrhages had occurred either as a result of the action of carbon dioxide on the vessels during the asphyxia of a paroxysm or because of increased intraventricular pressure. Yamaoka³⁴ reported three cases and suggested that angiospasm of the cerebral vessels bore a close relationship to the occurrence of convulsions.

According to Richer,³⁵ functional disturbances of the blood supply lead to lesions of the nervous tissue of a severity as great as one has been accustomed to attribute only to organic circulatory disorders, as in thrombosis and embolism.

Hiller and Grinker³⁶ report a case of a 3-year-old girl in whom the essential changes in the brain corresponded to softenings typically found associated with vascular occlusions. The striking observation was the tremendous dilatation of the cortical blood vessels within the softened areas, and their normal caliber in normal cortical areas. This is identical with what the authors found in carbon monoxide poisoning, and they feel that this is good evidence for stasis being the basis of the tissue damage. They go on to state that stasis in their case of pertussis could be objectively demonstrated, but that the reason for the development of this stasis was not obvious unless it was due, as in carbon monoxide poisoning, to the action of a circulating noxious agent on the vessel wall.

6. *Other Theories*.—Other theories have occasionally been mentioned in the literature. Thus, Hiller and Grinker discuss air embolism as a causative factor in the production of the cerebral manifestations. Neuberger³⁰ reported two cases and suggested that the changes were due to ischemic necrosis resulting from air emboli. Other authors have mentioned the similarity of the brain changes in pertussis with cerebral complications to those found in a woman dying of convulsions after coal gas poisoning.

It seems that the term pertussis encephalopathy, proposed by Jochims,³¹ covers most adequately these conceptions and, in the present state of our knowledge concerning the pathogenesis of central nervous system lesions in pertussis, should be the term of choice for the cerebral manifestations of the disease.

Of interest is the experimental work of Nakamura,³⁷ in which he attempts to demonstrate the significance of an exotoxin ("ausscheidende losliche toxin") of *Bacillus pertussis* as the causative agent in the production of meningoenceph-

alitis in rabbits. The same author reported that he was able to produce meningoencephalitis in rabbits with pertussis bacteria by damaging the liver function and elevating the temperature artificially.

Fonteyne and Dagnelie³⁸ caused convulsions and histologic changes similar to those found in human patients by injecting the endotoxin of *Hemophilus pertussis* intracerebrally and intrathecally into guinea pigs. Habel and Lucchesi⁶ state that convulsions occur in the spasmodic stage when paroxysms are severe. This, they reason, results in venous congestion of the head and neck with severe anoxemia. Most of the convulsive movements involve many groups of muscles, and localizing neurological signs are absent, supporting the theory of a generalized chemical or mechanical change in the brain. They claim that the immediate cause of death appears to be a generalized vasomotor collapse, probably due to the effect of cerebral anoxemia. However, they state, certain patients have a definite encephalitis as the underlying cause since convulsions do occur when paroxysms are mild and in the absence of other infections such as bronchopneumonia, as evidenced by the perivascular round cell infiltration.

With so many theories from which to choose, it is probable that no one completely answers all the questions of pathogenesis. We have been unable to observe pathologic pictures that would lend support to the "encephalitic" theory. Signs of central nervous system inflammatory disease have been conspicuous by their absence. It is our feeling that perhaps where such findings as perivascular or slight meningeal infiltrations have been found, these may very well have been the result of a concomitant and unsuspected viral disease.

On the other hand, the paroxysms of whooping cough are very real and dramatic. Peripheral cyanosis indicates vividly the types of vascular changes which may be taking place in the central nervous system. Petechiasis is a common visceral finding in anoxemia irrespective of the cause. With marked alterations in blood flow in the brain incident to paroxysms of coughing, it is not difficult to understand why petechial hemorrhages are such a frequent finding in pertussis. When the vessels are sufficiently weakened, massive hemorrhage may be the result of rhexis of these channels.

Summary of the Etiological Factors Responsible for the Cerebral Complications in Pertussis (Advanced by Various Authors).—

1. Vascular:

a. Hemorrhages

- | | |
|---------------|---|
| 1. Mechanical | } Gross, microscopic
Meningeal, cerebral, subarachnoid |
| 2. Toxins | |

b. Angiospasm and ischemia, resulting in nutritional death of brain cells

c. Anoxemia

d. Edema and congestion of the brain and meninges

2. Inflammatory:

a. Virus, activated by the disease

b. Bacterial

3. Air emboli, due to ruptured alveoli

4. Tetany

CLINICAL PICTURE

It is well to bear in mind that concomitant nonrelated pathologic findings may complicate the clinical picture in patients with cerebral manifestations in pertussis. We have encountered in our series five such cases. In one a glioma of the brain was found on post-mortem examination, and in four, bacterial meningitis was demonstrated. These cases were excluded from this report.

The clinical pattern of cerebral complications in pertussis is as follows:

1. Convulsions and coma:
 - a. Continuous or recurrent
 - b. Generalized or focal
 - c. Child may die in the attack.
 - d. Child may survive to become stuporous.
 - e. Coma may persist for days or weeks.
2. Paralyses:
 - a. Cerebral type:
 1. Motor: monoplegia, diplegia, hemiplegia, paraplegia
 2. Sensory: aphasia, deafness, and blindness
 - b. Spinal type:
 1. Spastic
 2. Flaccid
3. Meningeal syndrome
4. Neurological signs
5. Peripheral neuritis
6. Mental changes
7. Epilepsy

The most frequent symptoms at the onset in the cases studied were a rise in the temperature and an abrupt convulsion which was continuous or recurrent after a short pause. In most of the cases the onset of the convulsions was in the third or fourth week of the disease. These convulsions as a rule were generalized, but occasionally they were focal in character. The child may die in the attack, or survive to become listless, drowsy, and stuporous. The stupor or drowsiness may persist for days or weeks. Various neurological signs may manifest themselves during this time. Monoplegia, diplegia, hemiplegia, hyperreflexia, hyperspasticity, twitchings of muscles, and rigidity of various degrees may be found. Brudzinski, Kernig, and Babinski signs are almost always elicited. The pupils are frequently dilated and unequal, and hemorrhages in the eye grounds are found not infrequently. Temporary amaurosis and loss of speech were observed and recorded in the literature by one of us (A. M. L.). Bulbar palsies are occasionally encountered. The patients are unable to swallow, cannot hold up the head, mucus accumulates in the throat, and they cannot speak. Removal of the mucus by suction, and a high Trendelenburg position for postural drainage, continuous intravenous fluids of normal saline and glucose, and gavage feedings are essential in the care of such patients.

Some of these patients regain consciousness in a few days and recover without sequelae, while others may remain in stupor for weeks and regain consciousness slowly. Some of these die from intercurrent infections; others survive to develop sequelae.

TABLE VI. FREQUENCY OF SIGNS AND SYMPTOMS IN THE FORTY-SEVEN PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS IN PERTUSSIS

SIGNS AND SYMPTOMS	NUMBER OF TIMES FOUND
Convulsions	37
Stupor	14
Weakness of extremities	12
Hyperactive tendon reflexes	9
Nuchal rigidity	9
Cranial nerve involvement	8
Absent reflexes	7
Positive Babinski sign	6
Spasticity of extremities	5
Hemiplegia	4
Opisthotonos	4
Coma	4
Hypoactive tendon reflexes	3
Difficulty in speaking	3
Twitching of extremities	3
Papilledema	3
Blindness	3
Nystagmus	2
Strabismus	2
Difficulty in swallowing	2

PROGNOSIS

In our series of forty-seven cases there were nineteen deaths. The mortality rate was highest among children below 2 years of age (60 per cent). In this connection it must be remembered that the incidence of cerebral complications is highest in that particular age bracket, and accordingly one would expect a higher proportionate mortality. The general mortality rate in our series of cases was 40.4 per cent. In general, it may be stated that one-third of the patients with cerebral complications die in the acute phase; one-third recover to develop sequelae; and one-third recover completely. This coincides with the opinion of other observers.

SEQUELAE

In general, it would appear that the prognosis for a complete cure in whooping cough complicated by cerebral manifestations is not favorable. Thus, Eley³⁹ reported fourteen cases in eleven of which there were permanent injuries to the central nervous system, either in the form of mental retardation, paralysis, recurrent convulsions, or various combinations of these. In our series, mental retardation, paralysis, loss of visual acuity, and ataxia were noted. By far the greater proportion of our recovered patients were discharged from the hospital without apparent sequelae. Several authors have shown that the effects of pertussis encephalopathy may manifest themselves many years after apparent recovery. Eley³⁹ in 1930 reported four such patients, in whom the symptoms became manifest years after the attack of pertussis.

Among the more frequently reported sequelae are personality and behavior changes. In a very interesting paper, Lurie and Levy¹⁰ report a study of 243 children who had pertussis. Summary of their findings is as follows:

1. Five hundred children were studied in the Child Guidance Home, Cincinnati.

2. Two hundred and forty-three of these children had had whooping cough in the past.

3. Fifty-eight children had whooping cough at ages between 3 weeks and 2 years.

4. Thirty-four of these presented a definite relationship between neurological sequelae and behavior disorders and personality changes which occurred between $4\frac{1}{3}$ years and $17\frac{1}{3}$ years of age.

5. The following difficulties were noted:

a. General behavior problems	21
b. School maladjustment	8
c. General nervousness	5
d. Delay in onset of walking and talking	16
e. Convulsive seizures	9
f. Endocrine disturbances	9
g. Neuropathologic sequelae	25
h. Nerve deafness	15
i. Speech disorders	9
j. Abnormal electroencephalograms	5
k. Cortical atrophy on pneumoencephalograms	6

Two of the children had superior intelligence; eight were average; nine were subnormal; five were borderline; and two were feeble-minded. As for behavior changes, some were prepsychotic and some psychotic. Some had paranoid tendencies and visual and auditory hallucinations. Others had no interest in their appearance.

On the whole, the children studied fell into the following groups: Eight children were prepsychotic or psychotic; six children showed progressive intellectual deterioration; seventeen showed postencephalitic type of behavior with extreme motor restlessness, impulsiveness with a tendency to destructive activity and unpredictable behavior. Only a few of these showed intellectual retardation. Three of the children showed a type of behavior that was a combination of two or more of the preceding.

It is of interest to speculate whether personality and behavior changes may, in part at least, be due to cerebral atrophy following pertussis. That such cerebral atrophy does occur has been shown by Ford²¹ on post-mortem examination and also by Eley⁴¹ on pneumoencephalographic studies on his patients. Figs. 1 and 2 are reproduced from his article.* In Fig. 1, dilatation of the ventricular system is demonstrated, and in Fig. 2, cerebral atrophy, the most common sequela in cerebral complications of pertussis.

Visual disturbances, either temporary or permanent, may occur, and Litvak²² collected seventeen such cases and added one of his own. Among

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Fig. 1.—Patient admitted at the age of $4\frac{1}{2}$ years, for recurrent convulsions. Had a severe attack of whooping cough at the age of one year and convulsions at that time. Child showed opisthotonic position and generalized spasticity, was mentally retarded, and had a right-sided hemiplegia. Note the dilated ventricles bilaterally.

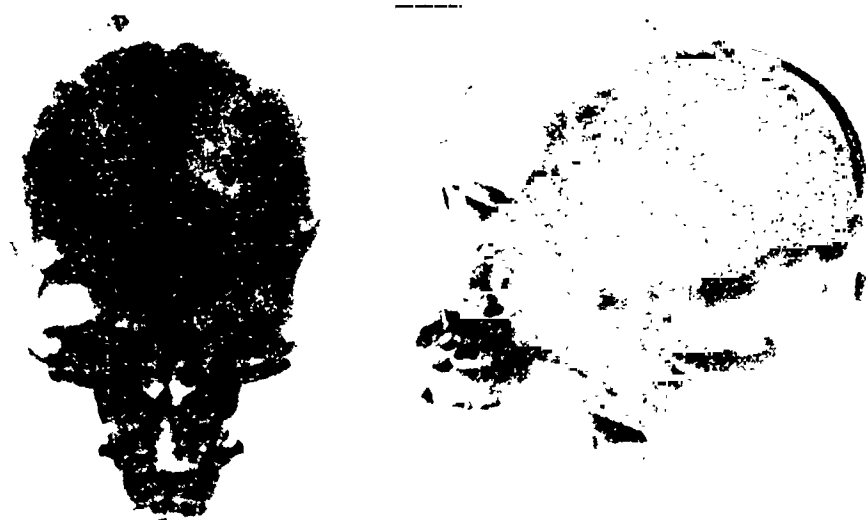


Fig. 2.—Child 10 months old, admitted because of inability to move left arm, left leg, and right arm. The patient had whooping cough at the age of one month. During the course of whooping cough she developed bilateral internal strabismus. One month prior to admission she became drowsy and was unable to use her left arm, left leg, and right arm. She did not recognize her parents and remained semistuporous. There was an old choroiditis in the eye grounds and the discs were blurred. Note the large, dilated, asymmetrical ventricles and cerebral atrophy.

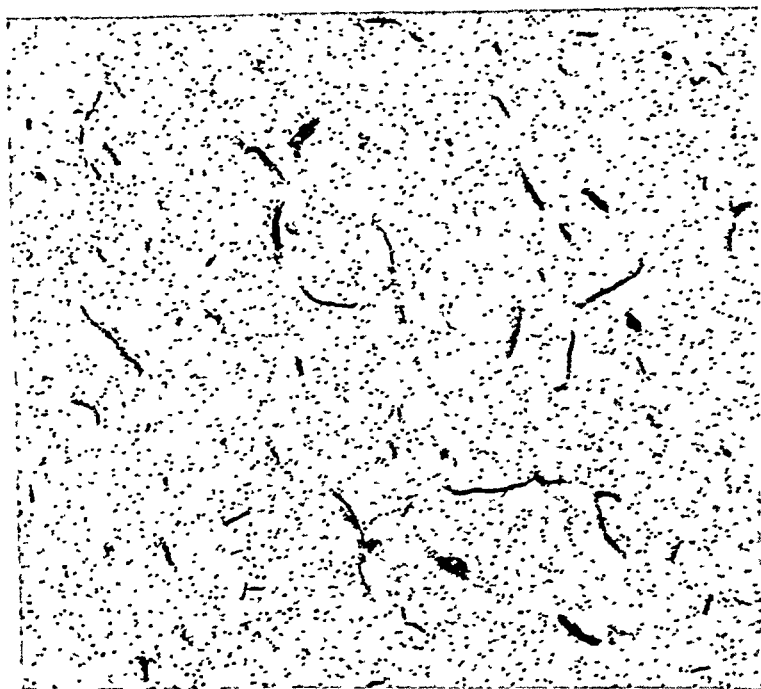


Fig. 3.—Pertussis. Marked congestion of vessels. (Hematoxylin and eosin stain, X80.)

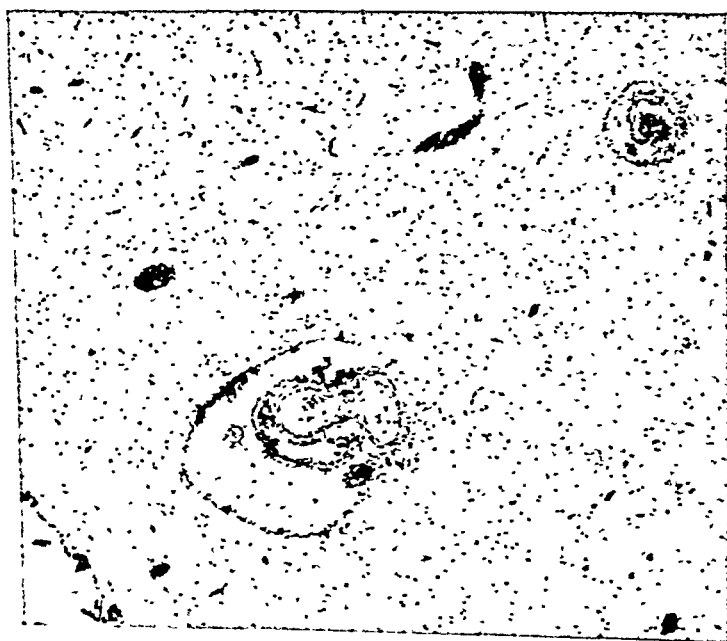


Fig. 4.—Section of brain showing hemorrhage into Virchow-Robin's space. (Hematoxylin and eosin stain, X80.)

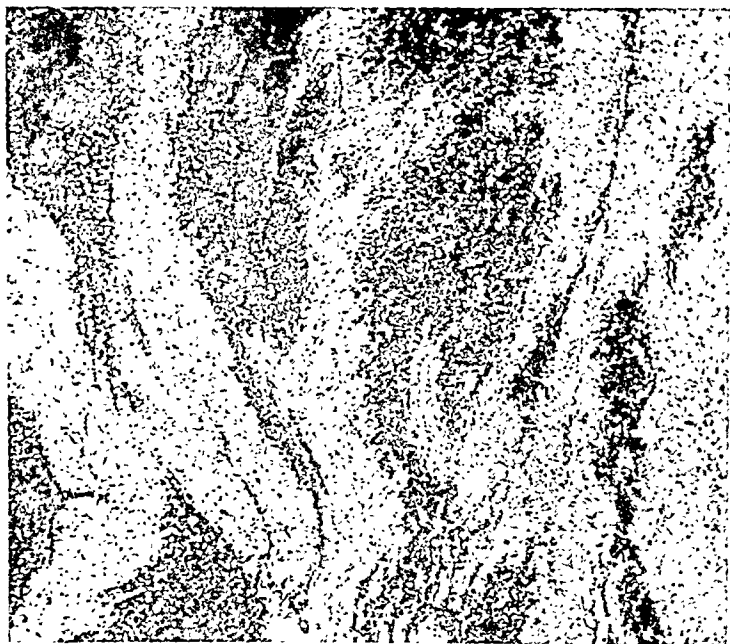


Fig. 5.—Section of brain showing diffuse hemorrhage. (Hematoxylin and eosin stain, $\times 80$.)



Fig. 6.—Section of brain showing thrombi in small vessels which are surrounded by extravasated blood. (Hematoxylin and eosin stain, $\times 80$.)



Fig. 7.—Section of brain showing massive subarachnoid hemorrhage. (Hematoxylin and eosin stain, $\times 80$.)

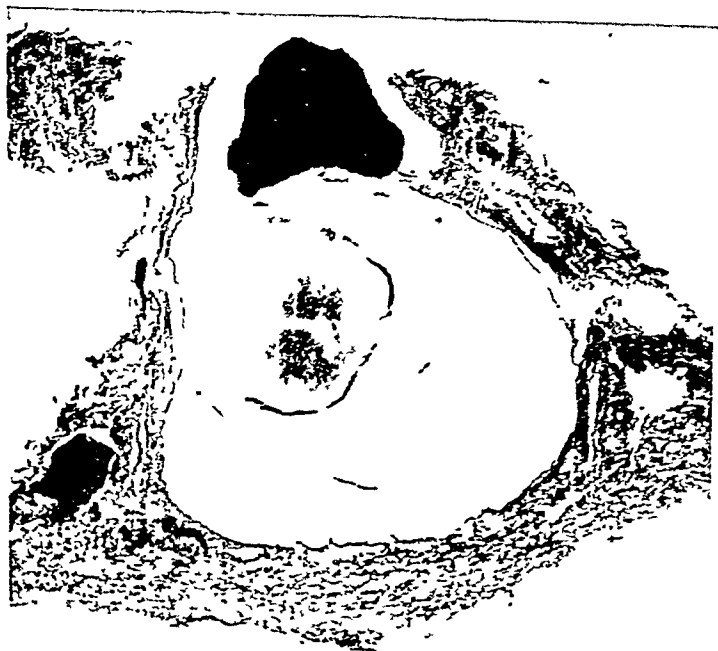


Fig. 8.—Section of brain showing thrombus in superior sagittal sinus of dura. (Hematoxylin and eosin stain, $\times 80$.)

these patients, two were permanently blind, thirteen had transitory blindness, and in two cases the ultimate results were unknown. Eley⁴¹ added two cases of visual disturbances after pertussis. Lazarus and Levine⁴² also reported a case of blindness. They felt that cerebral edema or acute hemorrhagic encephalitis accounts for the ocular changes in the majority of cases.

Sears⁴³ reported a case of right-sided hemiplegia, with eventual complete recovery. A case of hemiplegia was also reported by Cabot.²⁰ It is of interest to note that right-sided hemiplegia occurs more often than left, but the mortality rate seems to be higher in left-sided hemiplegia. Valentine¹ reported hemiplegia as occurring on the right side in twenty patients, of whom one died, whereas left-sided hemiplegia occurred in fourteen of his cases, with eight deaths. Grant and Williams⁴⁴ reported a case of left-sided hemiplegia and emphysema of the chest, neck, and cheeks. One year later, encephalography revealed gross atrophy of the right cerebral hemisphere with enlargement of the right lateral ventricle.

Cerebellar ataxia was reported by Kokken,⁴⁵ who states that this is a rare complication and that only four such cases have been reported. Hydrocephalus and macrocephalia were reported in one case by Camauer.⁴⁶

Eley⁴¹ also reported dilatation of the ventricles, diffuse cerebral atrophy, and calcified hemorrhages in a series of patients. Epilepsy as a sequela was reported by Worster-Drought.⁴⁷ This patient had pertussis at the age of 5 years. The epileptic seizures started five years after the original illness, and at the age of 16 years he still had epileptiform attacks.

FOLLOW-UP STUDIES

To date, we have succeeded in tracing twelve patients. The follow-up consisted of a detailed history regarding character, behavior, mental, physical, and social changes, if any, and a careful physical examination. The findings are summarized in Table VII.

The only conclusion that can be drawn from this follow-up series is that if pertussis is complicated by cerebral manifestations, it leaves the central

TABLE VII. FOLLOW-UP STUDIES ON TWELVE PATIENTS WHO HAD CEREBRAL COMPLICATIONS DURING WHOOPING COUGH

AGE AT TIME OF ILLNESS	AGE AT TIME OF FOLLOW-UP	INTERVAL SINCE ILLNESS	FINDINGS
7 weeks	3 years	2½ years	Normal
4 months	7 years	6 years, 8 months	Normal
5½ months	15½ months	10 months	Died of encephalitis of unknown etiology
7 months	20 months	13 months	Normal
8 months	6½ years	5 years, 10 months	Normal
1 year	4 years	3 years	Normal
14 months	4 years	2 years, 10 months	Repeated convulsions with every subsequent illness, no matter how mild
16 months	8 years	6 years, 8 months	Very "nervous"
3 years	13 years	10 years	Normal
3 years	3 years, 1 month	5 months	Ataxia
6 years	6 years, 2 months	2 months	Bilateral secondary optic atrophy
6½ years	15 years	8½ years	Petit mal seizures for five years after whooping cough

nervous system vulnerable to further injury. Thus, three of our twelve follow-up patients showed further convulsive episodes.

One patient remained normal for a period of ten months, then suddenly developed convulsions for which she was hospitalized at another institution. She died the day following admission. The diagnosis on the post-mortem findings was acute encephalitis of unknown origin.

One patient developed petit mal seizures following pertussis with cerebral complications. The attacks lasted for a period of five years, then suddenly ceased. He has been symptom-free for the past three and one-half years, attends high school, is a good student and a star basketball player.

Another child, now 4 years of age, has had repeated convulsive seizures with each subsequent illness. Thus, his measles was ushered in with a convulsion, he had an attack of bronchopneumonia complicated by convulsions, and each upper respiratory infection which has been accompanied by fever has also been accompanied by a convulsion.

A 3-year-old child developed ataxia which was of transient nature and showed considerable improvement after five months. One 6-year-old child, who became totally blind, gradually regained his vision, but when seen two months after discharge showed bilateral secondary optic atrophy.

One must remember that considerable time must elapse before the development of personality changes and behavior disorders appear.

Summary of Sequelae.—

1. Mental retardation
2. Various paralyses
3. Recurrent convulsions
4. Loss of visual acuity
5. Personality and behavior changes
6. Delay in walking and talking
7. Epilepsy
8. Idiocy
9. Blindness and deafness
10. Hemiplegia, diplegia, spastic paraplegia
11. Cerebellar ataxia
12. Hydrocephalus
13. Diffuse cerebral atrophy

PATHOLOGY

The pathologic changes occurring in the brain of patients with cerebral complications in pertussis are interrelated with the etiological factors causing these changes. Here, too, opinion is divided among pathologists as to whether the pathologic changes found in the brain are to be considered inflammatory, degenerative, toxic, or hemorrhagic.

Wechsler,⁴⁶ discussing the brain lesions in pertussis, states that in addition to the presence of an inflammatory reaction, the condition is also characterized by the predominance of hemorrhagic foci which are scattered throughout the cerebrum, the midbrain, in the region of the aqueduct, and in the pons and

medulla. Mikulowski³³ stated that the usual findings at autopsy are hyperemia, edema, congestion, and meningeal and venous thrombosis. Hiller and Grinker³⁶ in describing their patient state: "No thrombus or other organic obstruction to the vessels could be found, yet the essential pathology corresponds to the softening typically found associated with vascular occlusion. The type of lesion varied from ganglion cell 'Erbleichung' to incomplete and complete softening, which points to a slowly increasing diminution of the blood supply. Complete tissue death did not take place, as even the center of the focus revealed a proliferative ectodermal reaction. The striking observation was the tremendous dilatation of the cortical blood vessels within the softened area. This is identical with that which we find in carbon monoxide poisoning and speaks strongly for stasis as the basis of tissue damage." The autopsy findings in the case reported by Askin and Zimmerman²⁴ showed acute diffuse encephalitis and subarachnoid hemorrhages.

Canelli¹⁹ is of the opinion that focal hemorrhages, cerebral or meningeal, are very rare in pertussis, and that in all cases one may observe encephalitic lesions with a triad of pathologic findings—that is, hemorrhagic foci with necrosis, perivascular demyelination, and perivascular infiltration. Ford²¹ reports a case of a child, aged 20 months, with pertussis who developed cerebral diplegia. At autopsy there was found a great loss of cortical nerve cells unrelated to vascular disturbances or inflammatory processes.

Dolgopol,⁴⁹ after a careful analysis of fifteen autopsied patients at the Willard Parker Hospital, New York, sums up her findings as follows: "The changes in the brain in pertussis are apparently noninfectious. They are most likely of circulatory origin and consist of edema, ischemic cellular degeneration, multiple hemorrhages (usually small) and lymphocytic plugs in veins and capillaries. On rare occasions a 'secondary encephalitic' reaction may be observed in addition to the aforementioned changes."

Ford²¹ studied eleven patients with cerebral complications in pertussis. Ten of these patients died within a few days of the onset of the cerebral complications, and one lived several months. In one case he found a massive hemorrhage in the subarachnoid space; in three cases the cerebral vessels were intensely congested and innumerable minute hemorrhages were found scattered throughout the brain. He did not encounter softening or thrombosis and no inflammatory phenomena. Very little injury to the cortical cells or nerve fibers was noted. In one case in which the patient survived for six months there was general symmetrical wasting of the cortex which was most obvious in the frontal lobes.

In the course of this study, the brains of thirty-nine infants and children who died of pertussis were examined. Five of these were eliminated because post-mortem examination revealed a complicating meningitis in four patients and a glioma of the brain in one patient (Table VIII).

Gross examination in all instances showed congestion and edema, which was confirmed histologically. The cerebrospinal fluid was almost invariably increased in amount. Histologically, interfibrillary edema was often striking,

TABLE VIII. SUMMARY OF PATHOLOGIC MATERIAL STUDIED

MATERIAL	NUMBER
Pertussis patients on whom autopsy was performed	76
Brains examined	39
Brains excluded because of other complicating factors (Pneumococcic, streptococcic, tuberculous, and influenzal meningitis, and glioma of the brain)	5
Brains with pathologic changes due to pertussis	34
Brains with clinical diagnosis of pertussis encephalopathy	17

as was the marked capillarity of the brain. Dilatation of Virchow-Robin's space was often seen. These findings were not confined to any one area of the central nervous system.

Petechiasis, either gross or microscopic, was present in nineteen of the thirty-one cases. These punctate hemorrhages were variable in number, and were especially prominent in the pons, basal ganglia, and cerebrum. Often, the extravasation of blood was confined to Virchow-Robin's space, but in other instances, there was extension into the brain substance itself. Massive intracerebral hemorrhage was a rare finding, and subarachnoid hemorrhage was seen in only three instances. Thromboses were seen twice. In one case, there were multiple thrombi in small intracerebral capillaries and venules; in the other, there was a large thrombus obstructing the superior sagittal sinus of the dura mater. In some cases, small plugs composed of lymphoid cells were also noted. These were disregarded, however, because the effect of stasis and settling of blood in the cadaver could not be excluded as etiological factors in their production. (Table IX.)

TABLE IX. PATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM IN PERTUSSIS (34 CASES)

PATHOLOGIC CHANGE	NUMBER OF CASES
Congestion	34
Edema	34
Petechial hemorrhage	19
Subarachnoid hemorrhage	3
Thrombosis	2

At no time were perivascular or perineuronal collections of inflammatory cells seen. Infiltrations of the meninges, although carefully looked for, were also absent. These features are usually seen in association with infectious disease of the central nervous system. Their absence, therefore, was interpreted as indicating that the pathologic changes of the central nervous system in pertussis were largely the result of vascular phenomena rather than due to direct action on the brain of any toxin or actual bacterial invasion. The term "pertussis encephalopathy" is considered preferable to "encephalitis" for these reasons.

THERAPY

Therapy was essentially symptomatic, with sedatives, dehydrating measures, spinal punctures, transfusions, intravenous fluids, oxygen, human hyperimmune serum, sulfa drugs, penicillin, and ether and oil used as indicated. Avertin anesthesia was used in one case with apparent success. Various other therapeutic agents have been used and reported from time to time. Thus, Hyland,⁵⁰

Cruikshank,⁵ and others reported on the use of vaccine and convalescent serum. Neither appeared to be of benefit after the onset of the symptoms. The following is a summary of the therapeutic agents used by us in the treatment of the cerebral complications of pertussis:

1. Lumbar puncture
2. Sedatives: sodium phenobarbital, bromides, chloral hydrate
3. Ether 25 per cent in oil by rectum
4. Avertin anesthesia
5. Hypertonic glucose intravenously
6. Magnesium sulfate 50 per cent intramuscularly
7. Intravenous fluids
8. Transfusions
9. Oxygen tent
10. Human hyperimmune serum intramuscularly and intravenously
11. Gavage feedings
12. Sulfa drugs
13. Penicillin
14. Ascorbic acid
15. Calcium gluconate intravenously
16. Vitamin K

CASE REPORTS

A few typical case reports are presented:

CASE 1.—V. C., a white boy 6 years old, was admitted with a history of pertussis of three weeks' duration, complicated by pneumonia which had practically subsided at the time of admission. The day before admission the child developed a right facial paralysis and visual disturbances. Neurological examination showed a right supranuclear facial paralysis, scanning speech, normal reflexes, complete blindness with absent perception of light. There was weakness of the right arm and leg. The eye grounds showed a moderate bilateral papilledema. The remainder of the physical examination was negative. The temperature was 98.8° F. The spinal fluid was clear, pressure normal, protein 18 mg. per 100 c.c., globulin negative, sugar 55 mg. per 100 c.c., smear and culture negative, 2 cells both lymphocytes. The white blood count was 14,900 with 85 per cent lymphocytes. All other laboratory data were normal.

Two weeks after admission the child began to see light. The other symptoms gradually receded, although the vision remained impaired. Pallor of the optic discs, interpreted as secondary atrophy, became evident. The patient was discharged after five and one-half weeks, the only remaining symptom being markedly defective vision.

CASE 2.—B. K., a white female infant 3 years old, was admitted with a history of pertussis of four weeks' duration, and of bronchopneumonia of three days' duration. Examination revealed an acutely ill, prostrated child with signs of labored respirations and moderate cyanosis. The chest showed signs of bilateral bronchopneumonia. There were no other abnormalities noted. Temperature was 103° F., respirations 52. The spinal fluid was clear and under normal pressure. The cell count was 15, all lymphocytes, protein 60 mg., globulin negative, sugar normal, smear and culture negative. The blood white count was 33,600 with 81 per cent lymphocytes. Two or three days after admission the signs of cerebral involvement became manifest. There was constant aimless motion of the head and extremities, poor coordination of the eyes, sluggish reaction of the pupils, and diminished tendon reflexes. The eye grounds were normal.

The patient continued to run a stormy course with temperature ranging up to 104° F. The child was semicomatose and apparently completely blind and deaf. About one week after admission the chest began to clear and the child was removed from the oxygen tent. The pupils continued to react sluggishly, there was loss of control of the ocular muscles, and the reflexes remained hypoactive. Vomiting was marked. After three and one-half weeks, improvement was noticed. The child responded better to stimuli, the vomiting became less pronounced, the blindness and deafness improved. The child was seen again five months after discharge. At this time she was perfectly well except for a slight ataxia which later disappeared.

CASE 3.—I. L., a white girl, age 7 years, was admitted to the hospital with a history of pertussis of four weeks' duration and of four convulsions on the day of admission. Examination revealed an acutely ill, drowsy patient who responded to questioning. There was moderate nuchal rigidity and right supranuclear facial paralysis; the tongue deviated to the right; there was weakness of the right upper extremity, absent abdominal reflexes on the right side, bilateral Babinski signs, and hypoactive deep reflexes. The temperature was 102° F. The eye grounds were normal. The spinal fluid was clear, contained 5 cells, all lymphocytes, protein 40 mg., globulin negative, sugar normal, smear and culture negative. The white blood count was 20,700 with 65 per cent lymphocytes.

Intermittent convulsions continued for four days after admission. Weakness of the right lower extremity was noted. Because of the almost constant convulsions despite the usual sedatives, avertin therapy was instituted and continued for four days. This gave immediate and continued relief from the convulsions. There was continual gradual improvement, and the patient was discharged one month after admission without residual signs.

CASE 4.—A. W., white female infant, 10 months old, was admitted with a history of pertussis of two weeks' duration and of convulsions for twenty-four hours preceding admission. Examination revealed an acutely ill comatose infant. The extremities were flaccid. No other abnormalities were noted. The temperature was 102.2° F., pulse 150, respirations 40. The spinal fluid was clear, with pressure increased, and contained 10 cells, all lymphocytes; sugar was normal, smear and culture negative. The patient had several convulsions shortly after admission, but by the following day had regained consciousness. Convalescence was uneventful, and she was discharged two and one-half weeks after admission.

CASE 5.—W. B. W., male infant, age 8 months, was admitted to another hospital for diarrhea. During the course of treatment for the diarrhea a history of exposure to pertussis was obtained, questioning in this respect being prompted by the development of a croupy cough. The child was transferred to the Kingston Avenue Hospital. At the time of admission the temperature was 102.4° F.; the patient was dehydrated; the respirations were shallow and rapid. There were frequent paroxysms of cough followed by whooping. There was a transitory strabismus, nystagmus, and tremors of the left side of the body. Convulsions developed shortly after admission and remained continuous until the child died several hours after admission. The spinal fluid showed 4 cells, all lymphocytes.

CASE 6.—W. S., male infant, 7 months old, was admitted with a history of pertussis of two weeks' duration. He had a convulsion which lasted three minutes on the day of admission. On admission the child had a generalized convulsion which lasted six minutes. There were transitory strabismus and nystagmus. The spinal fluid was clear and contained 15 cells, all lymphocytes. The white blood count was 15,800 with 67 per cent lymphocytes. Convulsions continued on and off for the following eleven days in spite of therapy, and the child died on the eleventh hospital day.

SUMMARY

1. Over a period of fifteen years, 6,002 cases of pertussis were seen at the Kingston Avenue Hospital. Forty-seven of these were complicated by clinical cerebral manifestations.

2. (a) During the years 1932 to 1938 inclusive, 2,758 patients were admitted and 261 died, a general mortality rate of 9.4 per cent. Twenty-four cases were associated with cerebral complications. Six patients died, a mortality rate of 25 per cent.

(b) From 1939 to 1946 inclusive, 3,244 patients were admitted and 109 died, a general mortality rate of 3.3 per cent. Twenty-three cases were complicated by cerebral manifestations and thirteen patients died, a mortality rate of 56.5 per cent.

3. Of the forty-seven patients with cerebral complications, 28 survived and nineteen died, an average mortality rate of 40.4 per cent.

4. The onset of cerebral complications was almost always accompanied by convulsions and a sudden rise in temperature.

5. Fifty per cent of the patients who developed cerebral complications were under one year of age, and 60 per cent were under 2 years of age.

6. In 72.5 per cent of the patients, the onset of the cerebral complications occurred during the third and fourth weeks of the disease.

7. Spinal fluid studies were made in thirty-eight of the forty-seven patients. The findings were normal in all but eight cases. There was no correlation between the prognosis for life or sequelae and the spinal fluid findings.

8. The prognosis in patients with cerebral complications in whooping cough depends upon the age of the patient, the severity of the paroxysm, the nutritional state of the patient, the length of the convulsive seizure, the duration of the coma, and upon the presence of an associated complication.

9. In round figures, one-third of the patients with cerebral complications die, one-third recover to develop sequelae, one-third recover completely.

10. Twelve of the twenty-eight surviving patients in our series were followed over periods ranging from two months to eight years. Five (43 per cent) of them showed a tendency to further central nervous system manifestations.

11. The pathologic changes in the brains of thirty-four autopsied patients with cerebral complications were edema and congestion of the brain, petechial hemorrhages, subarachnoid hemorrhages, and thrombosis of cerebral veins and sinuses.

12. No changes of an inflammatory nature were observed.

13. The pathologic changes may be considered due to vascular disturbances or degenerative changes incident to anoxemia rather than inflammatory in origin.

14. The term "encephalopathy" appropriately covers these pathologic changes.

15. Treatment is entirely symptomatic. There is no effective specific therapy.

16. Present trends in age distribution of pertussis indicate a greater incidence in infants under one year of age.

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PEDIATRIC DEATHS IN A LARGE GENERAL HOSPITAL

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THIS inventory was undertaken with the conviction that it would serve as a stimulus for improving the quality of care given to our patients; the present report only sets a tentative pattern for subsequent periodic analyses. The year 1942 was selected because well-known handicaps existing in most hospitals at that time might be expected to accentuate certain problems ordinarily encountered in any hospital which cares for infants and children. Eleven members of our present pediatric staff have cooperated in reviewing all records of 436 fatalities which occurred among 12,470 admissions to the three pediatric and children's surgical divisions of the Charity Hospital at New Orleans. The authors have referred many controversies which arose during these reviews and accept responsibility for all designations employed herein. This material was gathered primarily for intradepartmental purposes; because no attempt has been made to compare it with Federal, State, or other hospital statistics, we felt free to deviate from conventional methods for handling vital data. The inferior quality of some clinical and pathologic studies in that year of wartime shortages occasionally called for arbitrary retrospective interpretations and has undoubtedly influenced some of our conclusions.

With few exceptions, patients were indigent residents of Louisiana. Critical perusal of records justified the conclusion that, in the light of present medical knowledge, at least 209 (48 per cent) of all deaths could be classed as inevitable at the time of admission. Nine of these patients were dead on arrival, forty-one were moribund and expired during the first hour of hospitalization, and the other 159 were proved to have conditions with inherently hopeless prognoses. We considered that thirty-seven (9 per cent) of these deaths might have been prevented had correct diagnoses been recognized earlier and proper therapy carried out. No such decisions as to preventability could be made for the remaining 192 deaths.

I. DEATHS IN THE NEONATAL PERIOD OF HOSPITALIZATION

As noted in Tables I and II, records indicate that 34 per cent of all pediatric deaths, and 80 per cent of all deaths in the neonatal period of hospitalization, occurred among infants who weighed less than 2.5 kg. at birth and were classed as premature. These premature infants were usually kept in the nurseries until a weight of 2.75 kg. had been attained, whereas mature infants usually remained only about five days. The fatality rate among premature infants was twenty-nine times higher than that among mature infants. One premature birth was

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reported for every seven and one-half mature births; this ratio was significantly higher for Negroes (1:7.4) than for whites (1:7.9), and for female (1:6.7) than for male children (1:8.5). The total death rate for all infants for any duration of stay in delivery rooms or nurseries was 36.8 per 1,000 live births, 29.1 for premature infants, and 7.7 for those who weighed more than 2.5 kg. at birth. Adequate explanations for the high percentage of premature births and the high total death rate during the neonatal period of hospitalization will require a more detailed analysis of obstetric and medical causes than is possible at present. The causes we have listed re-emphasize the importance of antenatal and natal factors; only about 20 per cent of all neonatal deaths could be ascribed to causes developing after delivery.

TABLE I. DEATHS AMONG INFANTS AND CHILDREN IN CHARITY HOSPITAL AT NEW ORLEANS, 1942

	DEATHS	ADMISSIONS	DEATHS PER 100 ADMISSIONS	DEATHS AS PER CENT OF ALL DEATHS
All neonatal	187	5,084	3.68	43.0
Premature	148	596	24.83	34.0
Mature	39	4,488	0.87	9.0
All others	249	7,386	3.37	57.0
Total	436	12,470	3.49	100.0

TABLE II. DEATHS IN THE NEONATAL PERIOD

	PREMATURE	MATURE	TOTAL NEONATAL	RATIO PREMATURE: MATURE
Born alive	596	4,488	5,084	1.0:7.5
Died	148	39	187	3.8:1.0
Percentage of deaths in specified group	24.8	0.87	3.7	29.0:1.0
Deaths per 1,000 live births	29.1	7.7	36.8	3.8:1.0

A. DEATHS AMONG PREMATURE INFANTS

Of 596 premature infants, 24.8 per cent died; all but two were born in the hospital, and these were admitted during the first day of life. Interesting variations were encountered when these deaths were expressed according to color and sex (Tables III, IV). Seventy-six and three-tenths per cent of all premature infants born and 72.3 per cent of those who died were Negroes; death rates were not significantly lower than for whites. Differences by sex were greater. Though there were only 2 per cent more total male births, there were 8.4 per cent fewer premature male births and 13.6 per cent more deaths among premature male infants. Explanations for this significantly higher percentage of deaths among male infants are inadequate; examination of birth weights by sex disclosed no remarkable differences.

If fifty-three infants weighing less than one kilogram were to be excluded as "previable" (Table V), we would attain a corrected neonatal mortality of 15.9 per cent among premature infants; similarly, if eighty-eight deaths under twenty-four hours were to be excluded (Table VI), another corrected figure would be 11.8 per cent. Of all deaths among premature infants, 12.8 per cent

TABLE III. DIFFERENCES BY RACE AND SEX AMONG PREMATURE INFANTS

	DEATHS AMONG PREMATURES		PREMATURES BORN		TOTAL LIVE BIRTHS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Race:						
White	41	27.7	141	23.7	1,253	24.6
Negro	107	72.3	455	76.3	3,831	75.4
Sex:						
Male	84	56.8	273	45.8	2,593	51.0
Female	64	43.2	323	54.2	2,490	49.0
Total	148	100	596	100	5,084	100
	(13.6 per cent more male prematures died)		(8.4 per cent more female prematures born)		(2.0 per cent more male live births)	

TABLE IV. PREMATURE MORTALITY

	DEATHS PER 100 PREMATURES	DEATHS PER 1,000 TOTAL LIVE BIRTHS
Race:		
White	29.07	32.72
Negro	23.51	27.93
Sex:		
Male	30.76	32.39
Female	19.81	25.70
Total	24.83	29.11

TABLE V. DEATHS AMONG 596 PREMATURE INFANTS BY CAUSE AND BIRTH WEIGHT

CAUSE OF DEATH	BIRTH WEIGHT					
	1,000 GM. OR UNDER	1,001-1,500 GM.	1,501-2,000 GM.	2,001-2,500 GM.	TOTAL NO.	PER CENT
Unspecified	41	20	18	9	88	59.46
Bronchopneumonia, etc.	3	6	5	2	16	10.81
Birth injuries	7	3	4	2	16	10.81
Syphilis	2	3	2	—	7	4.73
Malformations	—	2	3	2	7	4.73
Acute nutritional disturbance	—	—	2	2	4	2.70
Hemolytic disease	—	1	2	—	3	2.03
Other	—	2	2	3	7	4.73
All causes	53	37	38	20	148	100.00
Per cent	35.81	25.00	25.68	13.51	100.00	

TABLE VI. DEATHS AMONG 596 PREMATURE INFANTS BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH								TOTAL	
	UNDER 1 HR.	1-12 HR.	13-24 HR.	25-48 HR.	3-7 DAYS	8-14 DAYS	15+ DAYS		NUM- BER	PER CENT
Unspecified	12	37	8	15	8	3	5		88	59.5
Bronchopneumonia, etc.	1	1	2	1	1	1	9		16	10.8
Birth injuries	3	7	2	2	1	1	—		16	10.8
Malformations	2	2	—	2	—	—	1		7	4.7
Syphilis	—	5	—	1	—	—	1		7	4.7
Acute nutritional disturbance	—	—	—	—	—	—	4		4	2.7
Hemolytic disease	1	1	—	—	—	—	1		3	2.1
Other	—	4	—	—	—	1	2		7	4.7
All causes	19	57	12	21	10	6	23		148	
Per cent of total	12.8	38.5	8.1	14.2	6.8	4.1	15.5			
Per cent, cumulative	—	51.3	59.4	73.6	80.4	84.5	—			100.0

occurred within the first hour, 51.3 per cent within the first twelve hours, and 59.4 per cent within the first day. No such corrections are used, however, and all subsequent tabulations and remarks apply to uncorrected rates for all born alive and for any duration of stay in the delivery rooms or newborn nurseries. Leading causes for deaths are included in Tables V and VI, where they are related to birth weight and age at death, and in Fig. 1, where they are compared with those for mature infants.

Causes for eighty-eight of 148 deaths among premature infants were unspecified, that is, no conclusive clinical or pathologic opinion other than prematurity was ventured. Clinical and pathologic evidences of atelectasis and asphyxia vary only in degree among practically all premature infants who die; we felt justified in attributing only three deaths to the latter of these. Had we accepted varying degrees of atelectasis or asphyxia as adequate explanation for death, the large proportion due to unspecified causes would have been reduced. Two-thirds of the infants included in this category died within the first twenty-four hours, and about one-half of them weighed less than one kilogram. Causes for asphyxia, atelectasis, as well as death among these very small "previable" premature infants who died in the first twenty-four hours were presumably physiologic, though more careful clinical and pathologic studies might well have disclosed additional organic bases. The fact that 53 per cent of all deaths attributed to prematurity alone occurred in infants weighing more than one kilogram emphasizes the fallacy of employing birth weight as the sole index of viability or prematurity.

The presence of *bronchopneumonia* was verified by autopsy in seven of eleven instances, and good clinical bases justified such a diagnosis in the other four; the average age at death was thirty-one days. Added to this group were two deaths due to pulmonary abscesses complicating pneumonia, two attributed by pathologists to aspiration of vernix caseosa, and one to aspiration of vomitus. Low birth weights and feeding difficulties justify suspicion that repeated episodes of aspiration paved the way for most, if not all, of these respiratory causes, which accounted for about 11 per cent of all deaths among prematures.

Another sixteen of the deaths among premature infants were due to *birth injuries*; clinical diagnoses were confirmed by pathologic examination in fourteen instances. Only two of these babies survived longer than forty-eight hours.

Seven examples of *malformations*, accounting for about 5 per cent of the deaths, included esophageal and intestinal atresia, diaphragmatic hernia, hydrocephalus, anencephalus, meningomyelocele, and multiple cardiac and genitourinary anomalies. No corrective surgical procedures were justified, and only one of these infants survived longer than forty-eight hours.

Only one of seven *syphilitic* infants who died survived long enough to receive any specific therapy; in this one, inadequately treated, other infections hastened the fatal outcome. Characteristically extensive pathologic changes were described for each of these seven.

Four older premature infants died of *acute nutritional disturbances* for which no specific etiologic agent was discovered. Characterized by the all too familiar syndrome of diarrhea, dehydration, and acidosis, these disturbances

usually appear under a variety of causes in statistical tables. We have the conviction that, with few exceptions, disturbances in fluid and electrolyte balance are far more important causes of death than the various precipitating enteric and parenteral factors. Retrospectively, we feel that most of these deaths might well have been prevented had earlier and more intensive therapy been given.

Three infants had *hemolytic disease* (erythroblastosis fetalis). Two with characteristically severe clinical manifestations died shortly after birth; the third one survived the acute stage, only to succumb later from a complicating intercurrent infection. Pathologic examinations proved each of the diagnoses.

Among seven other deaths, two were ascribed to hemorrhagic disease and two to sepsis neonatorum. One of the latter had fulminating exfoliative dermatitis (Ritter's disease) with staphylococcal bacteremia; the other had multiple pathologic evidences of bacteremia, but this was not suspected during life. Finally, there were three infants in whom undoubted clinical and pathologic evidences of asphyxia were unaccompanied by organic disease.

In addition to the leading causes discussed previously, post-mortem examinations in 102 of the 148 fatal cases among premature infants revealed fetal atelectasis in sixty-three instances, infections in fifteen, and gross hemorrhages in six, as well as a number of minor lesions considered to be unimportant in explaining death. Twenty-six had pathologic changes suggestive of asphyxia. Though the relative importance of these secondary and incidental observations could not be assessed, their very number serves to re-emphasize the problems of differential diagnosis among premature infants.

B. DEATHS AMONG MATURE INFANTS

Thirty-nine deaths among 4,488 infants born at term accounted for about one-fifth of neonatal deaths and 9 per cent of all pediatric deaths. Autopsies were completed for twenty-four of these and yielded essential agreement with clinical diagnoses in seventeen. Data concerning leading causes for deaths appear in Fig. 1, where they are contrasted with causes among premature infants, and in Table VII, where they are related to duration of life. There were too few deaths to justify comparisons of diagnoses by conventional criteria, but it was interesting to note that here, as for premature infants, mortality was slightly higher for white than for Negro and for male than for female infants. Birth weights ranged from 2.5 to 4.42 kg., averaged 2.89 kg., and only three infants weighed more than 4 kg.

TABLE VII. DEATHS AMONG 4,488 MATURE NEWBORN INFANTS BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH							TOTAL
	1 HR.	1-12 HR.	13-24 HR.	25-48 HR.	3-7 DAYS	8-14 DAYS	15+ DAYS	
Birth injuries	2	2	5	2	1	-	-	12
Malformations	-	2	-	1	1	3	1	8
Unspecified	1	1	2	2	1	-	-	7
Bronchopneumonia	-	1	-	1	1	-	-	3
Hemolytic disease	2	1	-	-	-	-	-	3
Syphilis	1	1	-	-	-	-	1	3
Asphyxia	1	-	1	-	-	1	-	3
All causes	7	8	8	6	4	4	2	39

Autopsies performed in eight of twelve cases confirmed clinical diagnoses of *birth injuries*, and revealed gross intracranial hemorrhages in all but one. Dystocia, abnormal fetal positions, maternal toxemia or abruptio placentae apparently justified abnormal deliveries responsible for seven of these birth injuries; for the remaining five, no adequate reason for injury was found. Only one infant survived longer than forty-eight hours.

LEADING CAUSES OF DEATH in NEONATAL PERIOD of HOSPITALIZATION

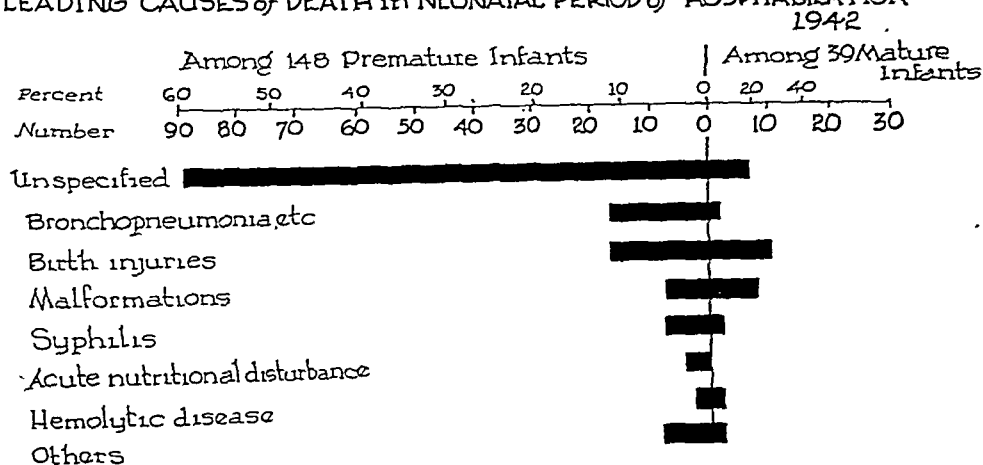


Fig. 1.

Eight deaths were explained by *multiple congenital malformations*. Most prominent among these were trilobulate heart, transposition of great vessels, evisceration of entire abdominal contents, gangrenous volvulus with malrotation of midgut loop, hydrocephalus with meningocele, tracheoesophageal fistula, urethral obstruction with severe bilateral hydronephrosis, and one cardiac anomaly which was not examined pathologically.

No satisfactory causes were established for seven deaths among mature infants; only one of these lived longer than forty-eight hours. Weakness, pallor, cyanosis, and disturbed respiratory patterns led to a number of conjectures regarding intracranial hemorrhage or the effects of various analgesics and anesthetics employed during labor. Five were examined pathologically, and only varying degrees of atelectasis were noted. Maternal complications required operative deliveries for four of the seven, and records indicate that there were adequate bases for suspecting fetal anoxia in these.

Pathologic diagnoses of *bronchopneumonia* were made for three infants who died in six hours, forty hours, and five days, respectively. The first of these had apparent respiratory paralysis; persistent dyspnea and recurrent strangulation in the others suggested that repeated aspiration of fluids and secretions contributed to the fatal outcome.

Three infants had clinically typical *hemolytic disease* confirmed pathologically; hydrops fetalis was the outstanding feature in two who died in less than

one-half hour. The third infant died at five hours of suspected intracranial hemorrhage, and autopsy revealed extensive extramedullary hematopoiesis and multiple visceral hemorrhages. Three deaths occurring at one-half hour, seven hours, and seventeen days after birth were attributed to *congenital syphilis*; two of these infants also had severe hemorrhagic manifestations. Characteristic clinical features of asphyxia were encountered in three infants with no discernible organic abnormalities. Post-mortem examinations done for two were confirmatory.

In addition to these causes, included in Table VII and Fig. 1, which were in each case considered to be the most logical single explanation for death, many other abnormalities were encountered. These included fourteen examples of fetal atelectasis, five serious infections, four gross hemorrhages, and two important congenital anomalies. Pathologic evidences of asphyxia were noted in nine of twenty-four autopsies.

II. OTHER DEATHS

Among 7,386 admissions other than those included in the previous section, were ten newborn infants delivered elsewhere but admitted to this hospital after twenty-four hours, together with all other patients admitted before their twelfth birthday. As shown in Fig. 2, 27 per cent of these patients were under one year and 42 per cent under 2 years of age when admitted. The percentage of total admissions declined further in the next year, and then remained at a level varying but slightly from 5 per cent. There were 249 deaths. Comparing percentage distribution for these, a sharp fall is noted after the first year; irregularities in the percentage of deaths during each year of age after the

TABLE VIII. DEATHS AMONG INFANTS* AND CHILDREN TO AGE TWELVE BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH					TOTAL TO AGE TWELVE	
	BY MONTHS UNDER AGE TWO			TOTAL UNDER	TOTAL OVER		
	0-6 MO.	7-12 MO.	13-24 MO.	AGE TWO	AGE TWO	NUM- BER	PER CENT
Pneumonia, etc.	37	10	4	51	5	56	22.5
Meningitis	13	8	1	22	5	27	10.9
Acute nutritional disturbance	20	2	2	24	0	24	9.7
Accident	0	1	0	1	21	22	8.9
Malformations	11	5	2	18	3	21	8.4
Tuberculosis	4	1	3	8	9	17	6.8
Syphilis	13	1	0	14	0	14	5.6
Intestinal obstruction	4	2	0	6	3	9	3.6
Pertussis	2	4	1	7	2	9	3.6
Bacteremia	2	0	1	3	5	8	3.2
Rheumatic fever	0	0	0	0	7	7	2.8
Diphtheria	0	0	1	1	5	6	2.4
Diseases of the ear	4	1	0	5	0	5	2.0
Malignancy	0	0	1	1	3	4	1.6
Appendicitis	0	1	1	2	1	3	1.2
Tetanus	0	0	0	0	2	2	0.8
All other causes	5	0	2	7	4	11	4.4
Unspecified	3	0	1	4	0	4	1.6
All causes	118	36	20	174	75	249	100.0
Per cent of total				69.9	30.1	100.0	

*Excluding neonatal period of hospitalization.

fourth are explained on the basis of comparatively small numbers—altogether, deaths occurring beyond the fifth year accounted for only about 10 per cent of the total number. Almost 40 per cent of all these deaths were considered to be unpreventable, that is, the patients were dead on arrival, died in the first few minutes after hospitalization, or were discovered to have diseases for which no effective therapy could be offered. Leading causes for death, and their relative importance before and after age 2, are shown in Fig. 3 and Table VIII.

DISTRIBUTION OF ADMISSIONS AND DEATHS AMONG SICK INFANTS* AND CHILDREN

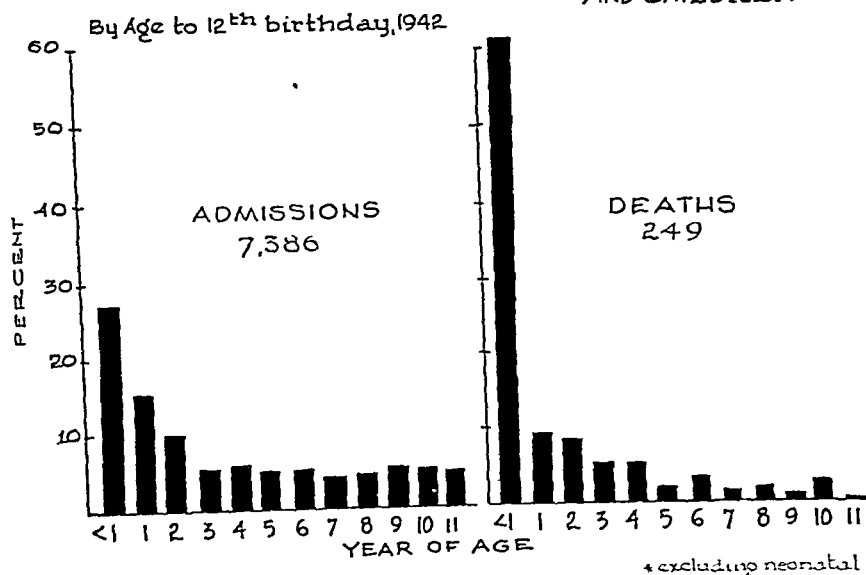


Fig. 2.

In contrast with premature and mature infants, mortality was slightly higher among the Negro than the white and among female than male children. Reasons for these statistically insignificant differences have usually been veiled in generalities concerning environmental considerations, and we discerned no better explanations.

A. DEATHS UNDER TWO YEARS

Sixty-one per cent of all deaths beyond the neonatal period of hospitalization occurred during the first year and 70 per cent before the second birthday (Fig. 2). Sixty-eight and four-tenths per cent were in Negroes and 55 per cent were in male children. Distribution by age and leading causes is shown in Table VIII; over 88 per cent of deaths in this younger group occurred before the first birthday. Tabulation by calendar months showed that the smallest number of deaths and admissions fell in July, August, and September. Considering the relatively small number of deaths attributed to each cause, we could establish no distinct seasonal pattern for specific diagnoses in this single year.

The period of hospitalization for fifty-one patients who died of primary respiratory disease (bronchopneumonia) varied from a few minutes to as long as twenty-five days. Twenty-two of them lived less than twelve hours. The number of cases was too small to permit conclusions regarding comparative prognoses by specific etiology. Three examples of acute laryngotracheobronchitis, presumably due to mixed infection, were included. Acute and chronic nutritional disturbances, bacteremia, congenital anomalies, and extrapulmonary infections appeared frequently as important contributory factors; only one example of empyema was recognized.

LEADING CAUSES OF DEATH IN CHILDREN TO AGE TWELVE (1942)

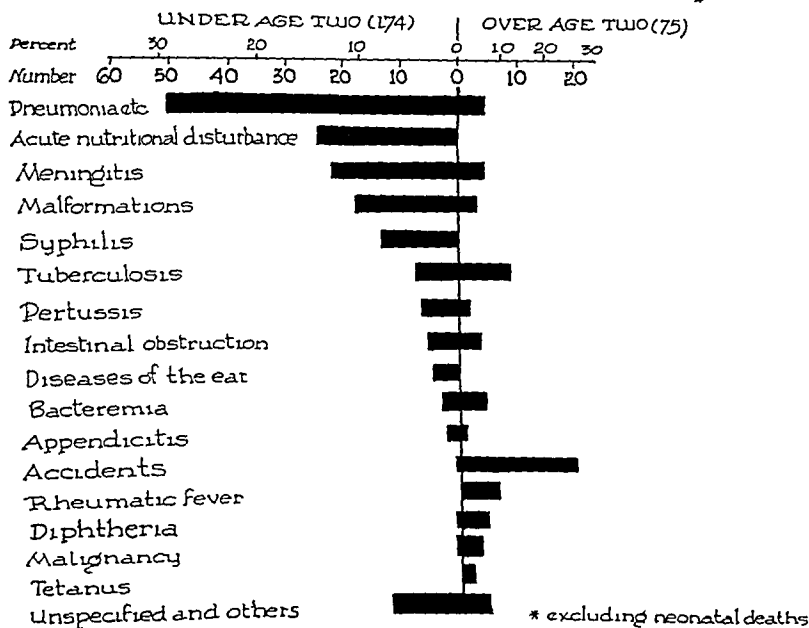


Fig. 3.

In this younger group, *acute nutritional disturbances* ranked second in importance. Among twenty-four of these, there were a variety of initiating or aggravating factors, including specific and nonspecific respiratory diseases, otitis media, or other parenteral infections, and three cases of specific enteritis due to organisms of the *Shigella* group. Certainly, many children whose deaths were attributed to other causes had similar but milder fluid and electrolyte disturbances. For each of these twenty-four infants, however, the acute nutritional disturbance seemed more logically responsible for death than the initiating parenteral or enteric cause.

Among twenty-two deaths due to *meningitis* other than tuberculous, *Hemophilus influenzae* was responsible ten times, pneumococcus eight times, meningococcus twice, streptococcus once, and no organism was isolated in one instance.

The duration of symptoms before hospitalization was extremely long, averaging eleven and one-half days; half of these patients had symptoms of meningitis for more than ten days when admitted, and only seven of them for less than five days. The far-advanced character of the disease was further suggested by agreement that hopeless prognoses were justified for ten of these patients at the time of admission.

COMPARISON OF CLINICAL AND POSTMORTEM DIAGNOSES

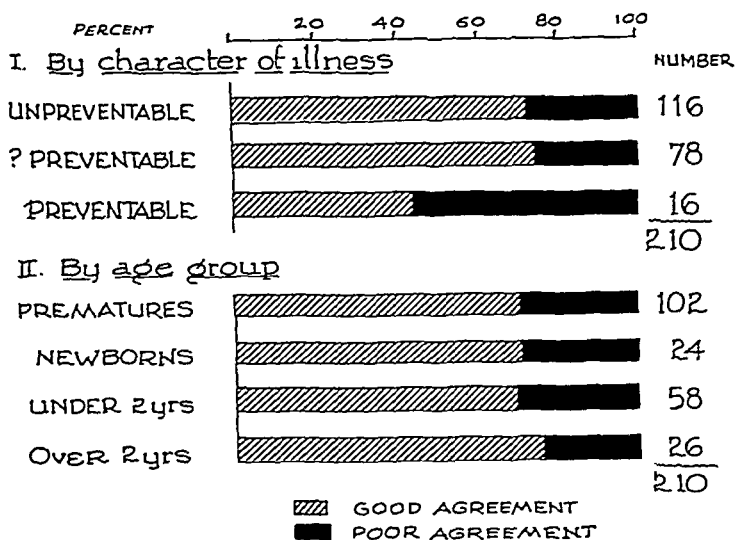


Fig. 4.

Eighteen died of *congenital anomalies*; these were characteristically multiple, but the ones judged to be most important in explaining death were found in the genitourinary system eleven times, in the central nervous system eight times, in the heart seven times, and in the gastrointestinal tract twice. The oldest patient included in this category died at thirteen months, and only seven of the infants survived for more than six months.

There were fourteen deaths attributed to *congenital syphilis* among thirty-six infants hospitalized for this disease. Usual therapy consisted of varying combinations of arsenicals and bismuth, which appeared to hasten death in at least five. The average age at death was 15 weeks, with a scatter from 7 to 36 weeks; none had been treated for syphilis prior to hospitalization.

All of eight deaths from *tuberculosis* were classed as unpreventable; no effective medical therapy could be offered for widespread involvement present at admission. In six of these, meningeal lesions predominated; all had military and extensive pulmonary disease. We have previously emphasized the importance of tuberculosis as a cause for death in infants and children at our hospital

and pointed out that during the last decade it accounted for 9.8 per cent of all deaths at this hospital and 6.1 per cent of deaths in children.¹

Pertussis, in each case accompanied by bronchopneumonia, was responsible for seven deaths among seventy-nine patients hospitalized for this disease. All seven deaths occurred between the ages of 3 and 13 months, five of them early in the third week of the disease and the other two in the seventh and ninth weeks. There is no doubt that many others were recognized and treated in out-patient departments.

There were six fatalities among fourteen infants admitted for *intestinal obstruction*. Three were due to intussusception; in each instance typical symptoms had been present for more than six days before hospitalization. One was ascribed to incarcerated inguinal hernia, one to volvulus and gangrene after postoperative adhesions, and one to extrinsic duodenal obstruction.

Direct extension of infection, infections elsewhere in the respiratory tract, or acute nutritional disturbances made it difficult to attribute death primarily to *otitic disease*, but we found no alternative for five examples so included in Table VIII and Fig. 3. Two deaths from *appendicitis* followed prolonged illness, spontaneous rupture, and generalized peritonitis; both patients were moribund at admission, and neither responded to diligent therapy.

Three examples of *bacteremia* included one due to *Staphylococcus aureus*, with numerous visceral abscesses, one due to an unidentified gram-positive bacillus, and one presumptive, manifested by extensive furunculosis in a debilitated infant. There was only one death from *diphtheria* under age two, one attributed to *aspiration of feeding*, one to *cerebellar astrocytoma* in an infant of 16 months. Included among deaths due to all *other causes* were three examples of intracranial hemorrhage, two following birth trauma in infants delivered outside the hospital and one occurring spontaneously in the course of an upper respiratory infection. There was one case of acute bacterial endocarditis in an infant of six weeks, one of severe hemolytic disease (erythroblastosis), one of primary peritonitis and one of acute leukemia. There were four unexplained deaths, each occurring so soon after admission that no satisfactory diagnostic studies were made.

B. DEATHS AFTER AGE TWO

Thirty per cent of 249 deaths beyond the neonatal period of hospitalization occurred in children who had passed the second birthday, and 59 per cent of these were less than 5 years of age when admitted. Fifty-six per cent were Negro, and 57 per cent were male. Distribution of admissions and deaths by age are shown in Fig. 2, and leading causes for death in Fig. 3 and Table VIII. Because of the small number who died of any single cause in this age group, comparisons by sex, color, and age were not made. Forty per cent of these deaths after the age of 2 were considered to be inevitable at the time the patients were admitted.

Accidents, accounting for twenty-one deaths, led the list of causes beyond age two. There were seven patients with extensive burns, three with crushing injuries, three examples of acute lead poisoning; two were attributed to an

anesthetic or its immediate sequelae, two to aspiration or ingestion of foreign body, two to trauma leading to intracranial hemorrhage, one to gunshot wound, and one to drowning.

Tuberculosis was responsible for nine deaths. Only pulmonary lesions were demonstrable in four patients, and the other five had extensive visceral involvement with meningitis predominating. The shortest duration of symptoms recorded before hospitalization was two weeks, the longest two years, and the mean duration was about six months. Tuberculosis was suspected or proved at the time of admission for six, when four of these deaths were considered unpreventable. The average duration of hospitalization was seven days, with a range from ten minutes to fifteen days, emphasizing again the often fulminating course of reinfection forms of this disease in children.

Three of seven deaths due to *rheumatic fever* with heart disease occurred during the fourth year of life; the oldest patient was 11 years old. Diagnoses, apparently satisfactorily established by clinical criteria, were proved pathologically for four who were examined at autopsy. The average duration of hospitalization was thirty-five days; the total duration of illness varied from two weeks to six and one-half years. All patients were lifelong residents of this State. During this same year, diagnoses of rheumatic fever and heart disease were made for seventy children in this age group.

Among five deaths due to *bronchopneumonia*, one followed severe laryngo-tracheobronchitis, one was accompanied by lung abscess, and one by bronchopleural and esophagopleural fistulae complicating empyema. Five children died of *diphtheria*, all under 6 years of age; four had predominantly laryngeal involvement, and two died within an hour of arrival at the hospital. All were promptly recognized and all received diligent specific and supportive therapy.

Among five deaths from *acute purulent meningitis*, one was due to *Staph. aureus*, one to pneumococcus type VI, and no organisms were recovered from the other three. The second of these appeared to be due to extension of otitic disease, but no adjacent foci were found for the others. Closely related to the last group were five examples of *staphylococcal bacteremia*; three of these patients had terminal meningitis. One was associated with exacerbation of chronic osteomyelitis, one with cavernous sinus thrombosis, and one with a sickle-cell crisis.

Of three deaths from *intestinal obstruction*, two were due to intussusception, the other to adhesive bands following an earlier surgical procedure. Among three *congenital anomalies* responsible for death, two were cerebral and one cardiac; all patients were chronically invalidized and had terminal respiratory infections. *Malignancies* ranked next, with one retinal glioma, one craniopharyngioma, and one unidentified but inoperable cerebellar tumor. Both children who died of *pertussis* had extensive bronchopneumonia, and one of them had accompanying acute hemorrhagic nephritis with cardiac failure. Both cases of *tetanus* followed deep puncture wounds, were far advanced at the time of admission, and failed to respond to appropriate therapy. Death of one child was attributed to *appendicitis* complicated by peritonitis, subdiaphragmatic abscess, fecal fistula, and extreme cachexia.

Among four deaths from other causes, one was ascribed to measles with bronchopneumonia, one to acute nephritis with cardiac failure, one to chronic adhesive pericarditis (Pick's syndrome), and one to aspirational pneumonitis following corrosive esophagitis.

COMPARISONS OF CLINICAL AND POST-MORTEM DIAGNOSES

Clinical diagnoses were compared with those recorded after autopsy, and grades were assigned for degrees of agreement. Crude correlations could then be made according to a number of variables. We found that pathologists confirmed clinical diagnoses for cause of death, with occasional minor and incidental additions, in from 70 to 75 per cent of the cases they examined. No significant change in quality of clinical diagnoses could be related to age of patients or duration of symptoms before admission, though correlations improved with duration of hospitalization; good agreement was observed in 66 per cent of patients who had been hospitalized for less than one week but increased to 82 per cent in those hospitalized for more than one week. Little point would be served by including here all the data and charts from which such comparisons were made; only a sample is included as Fig. 4. As one would expect, poorest agreement of clinical and post-mortem diagnoses was obtained for deaths we had classified as preventable. Unfortunately, autopsies were secured for only 51 per cent of all pediatric deaths that year. Though our grading of correlations may have been severe, and the number of cases small, it was both stimulating and disappointing to find that autopsies revealed clinically unrecognized major lesions or unsuspected causes for death in the large percentage indicated as "poor agreement" in Fig. 4.

SUMMARY

During 1942 there were 436 deaths among 12,470 children admitted under age 12. Forty-three per cent of all pediatric deaths occurred during the neonatal period of hospitalization for 5,084 infants born alive in the hospital; this group constitutes the basis for the first portion of our study, in which premature and mature infants are considered separately. The second portion is concerned with the remaining 57 per cent of all pediatric deaths among 7,386 infants and children from one day to 12 years of age at the time they were admitted; here patients younger and older than 2 years of age are considered separately.

Leading and incidental causes for death, and pertinent differences by age, race, and sex were analyzed and discussed for each group. Finally, crude correlations of clinical and post-mortem diagnoses were made for 210 patients examined pathologically.

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NONTUBERCULOUS PULMONARY CALCIFICATION

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THE conception that calcium deposits in the lungs or at their hili are pathognomonic of tuberculosis has long been well established in the minds of medical men, both clinicians and roentgenologists. In recent years much evidence has been accumulated to show that there are other common causes of pulmonary calcification.

Gass¹ conducted a careful study of 1,281 children in Tennessee and found many with negative tuberculin tests and calcified hilar glands. He made no effort to explain this discrepancy. Long and Stearns,² after reviewing over 40,000 chest films of American soldiers with calcium deposits in the chest, reported that the incidence of such deposits varies in different localities and is greatest in the East Central United States. They concluded that the great majority of the cases of pulmonary calcification were due to tuberculosis but that some were due to fungus diseases.

Lumsden and Dearing³ conducted a careful and extensive study in several counties of five South Central States. In Giles County (Tenn.) alone, they found 14,000 persons with calcium deposits in the chest and only 10,000 with positive tuberculin tests. Even more striking is the fact that they found a much higher incidence of pulmonary calcification in some of these counties than in others where conditions relative to tuberculosis seemed to be the same. A county with a high incidence of pulmonary calcification often lay next to one with a low incidence. Those counties with a high incidence of pulmonary calcification are underlaid with limestone (with a high percentage of calcium in the drinking water), whereas those of low incidence are underlaid with a flint type of rock. These soil conditions were determined by the U. S. Geodetic Survey. These facts suggest that one must consider factors other than disease.

Olson⁴ observed a high incidence of pulmonary calcification in Ross County (Ohio), which could not be accounted for by tuberculosis. He concluded that these cases were due to a common unrecognized disease, perhaps ascariasis. But he could produce no definite evidence of this. This study was based on the observation of 500 individuals. An unusually careful study was conducted by Aronson⁵ of the Phipps Institute among North American Indians. He found, as part of his study, that in the Pima Agency of Arizona alone there were 704 children with negative tuberculin tests. Of these, 102, or 14.5 per cent, had calcified hilar nodes. These were not false negatives due to anergy, because one year later he produced a positive tuberculin test in fifty-six out of sixty-two such children by the injection of BCG vaccine, that is, attenuated live tubercle bacilli. He concluded that these nontuberculous calcium deposits may be due to *Coccidioides immitis* infections. Geever⁶ suspected that tuberculosis is not the only cause of pulmonary calcification.

¹From the Pediatric Department and the Bronchoscopic Department of St. Luke's Hospital, Chicago.

Palmer⁷ reported a study of 3,105 student nurses, conducted cooperatively by the National Tuberculosis Association and the United States Public Health Service. Of this total number, 294 had pulmonary calcification. Approximately 80 per cent of these were tuberculin negative and were regarded as not having tuberculous infection of any sort. A high percentage of these had a positive skin reaction to histoplasmin. The author concluded that the calcification was probably due to a mild subclinical infection with *Histoplasma capsulatum*.

Our own series, though small, has been studied intensively and in a somewhat different manner. Our curiosity was aroused by children with negative tuberculin tests and calcium deposits in the chest. By chance, fourteen such children were encountered in the outpatient department. All 14 were tuberculin tested with PPD (purified protein derivative of Seibert⁸). They were completely negative to both first test strength and second test strength PPD. They were rechecked a year later not only by these two tests but also by the Vollmer patch test. The PPD tests are generally regarded as the most accurate of all tuberculin skin tests. The fourteen children were consistently negative to all these tests.

Bronchoscopy.—In order to further rule out the possibility of false negatives, all fourteen were bronchoscoped. The appearance of the mucous membrane was studied and recorded. The bronchial secretion was aspirated and studied by direct smear, culture, and guinea pig injection. The mucous membrane at the bifurcation and in the main bronchi in nine out of the fourteen was described as somewhat abnormal. Some portions of the inspected areas were slightly reddened, thickened, or edematous. These changes were neither striking nor characteristic of any known disease.

Bacteriology.—Acid-fast bacilli were found by direct smear in the aspirated secretion from only one patient, although careful search was made for them in each. This patient was a child with the typical clinical characteristics and laboratory findings of Boeck's sarcoid. This rare disease is regarded by some investigators as a tuberculous-like disease, by others as a mild, atypical, hard tuberculosis with anergy to the tuberculo-protein. This disease, therefore, has a negative tuberculin reaction. Admittedly, it is difficult to demonstrate acid-fast bacilli in Boeck's sarcoid. We feel that the findings in this case are some evidence of the efficacy of the bronchoscopy method of study.

In every case except one, the aspirated secretion was injected into a guinea pig. Ten of these thirteen pigs lived the usual eight weeks, were killed and autopsied, but none had tuberculosis. The other three died prematurely of other infections. Fusiform bacilli and spirochetes were demonstrated by direct smear of the aspirated secretion in eight cases.

X-ray Study.—Calcium deposits were demonstrated at one or both hili in every patient. One patient showed calcification in the right third interspace not unlike a Ghon tubercle. The calcium deposits were not heavy in any patient.

Other Laboratory Data.—The red, white, and differential blood counts and hemoglobin estimations were in the normal range. Urinalysis and complement fixation tests for syphilis were negative for every child.

Clinical Data.—These children were both Negro and white, male and female, with ages ranging from 3 to 14 years (average 8). Only one had had known exposure to tuberculosis. Eight of these children had a history of frequent colds with a cough that was usually described as persistent or chronic. These children were all well nourished and appeared normal to cursory inspection.

Histoplasmin Skin Tests.—Histoplasmosis is usually considered a rare and serious infection. However, the fact that a large number of persons without history of serious disease are skin sensitive to histoplasmin raises this question: May there not be an unrecognized subclinical form of histoplasmosis detectable only by skin test?

Twelve of these fourteen children were skin tested with histoplasmin. Each was injected intradermally with 1/10 c.c. of diluted histoplasmin prepared in the laboratory of St. Luke's Hospital from an individual with a fatal infection with *Histoplasma capsulatum*, reported by Van Pernis and co-workers.⁹ The technique of preparation is outlined in their report. The site of injection on the forearm was observed for one hour for immediate reaction and after twenty-four hours for delayed reaction. The formation of a 10 mm. wheal or skin induration with redness was considered a positive reaction. Such a wheal appeared in six of the twelve children. In each of the six positive cases the indurated area varied from 1½ cm. to 2½ cm. with a red area usually extending well beyond the induration and ranging up to 4½ cm. in diameter.

This reaction in all six patients occurred within one hour, usually within fifteen minutes. In two of the six patients, induration and redness were still present after twenty-four hours. In the other four, they had disappeared by the second day. None of the six had a delayed reaction, that is, one appearing on the second day.

SUMMARY

We have presented fourteen children with clearly negative tuberculin tests. One child had Boeck's sarcoid involving the lungs without cough. Acid-fast bacilli were demonstrated by direct smear in the secretion aspirated through the bronchoscope in this one patient only.

On the basis of this as well as other experiences, we regard bronchoscopic methods of study in questionable cases of tuberculosis as very valuable.

All remaining thirteen children with negative tuberculin tests had small but definite calcium deposits in the chest. A thorough clinical study, including bronchoscopy and bacteriologic study of the aspirated secretions, failed to produce any evidence that these children had or had had a tuberculous infection.

Eight of these thirteen patients with pulmonary calcification had some change in the mucous membrane at the bifurcation or in the main bronchi. Eight of the thirteen had a history of frequent colds or persistent coughs. Twelve of the thirteen were skin tested for histoplasmin. Six of these twelve gave an immediate reaction to histoplasmin. There were no delayed reactions.

CONCLUSIONS

On the basis of reports in the literature and our own experience, we feel justified in concluding definitely that there are important causes of pulmonary

calcification exclusive of tuberculosis. It is generally recognized that tuberculosis is not the sole major cause of calcification in other parts of the body. Why should the chest be an exception? We believe tuberculosis is the most frequent cause of calcium deposits in the chest. However, the other causes are not rare or inconsequential. They should *not* be ignored as they have been in the past.

Just what these other causes are, is a question still not completely answered. There is suggestive evidence that a mild subclinical histoplasmosis may be one of them. Ordinary recurrent respiratory infections may be another.

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RECEDING CHIN AND GLOSSOPTOSIS

A CAUSE OF RESPIRATORY DIFFICULTY IN THE INFANT

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ONE of the causes of cyanotic attacks in newborn infants which is commonly overlooked is hypoplasia of the mandible, or receding chin, occasionally referred to by the name of Pierre Robin syndrome. This condition, described in 1929 by Pierre Robin,¹ is often found in association with cleft palate, foreshortening of the genioglossi muscles, and inspiratory retraction of the sternum.

In hypoplasia of the mandible, ptosis of the tongue causes mechanical obstruction of the larynx with cyanosis, difficulty in swallowing, marked respiratory embarrassment with severe retractions of the sternum, and subsequent malnutrition. The symptoms are aggravated during feeding.

The clinical picture resembles that of true obstructive laryngeal dyspnea and is caused by mechanical obstruction. The infants may die of starvation, called glossoptotic cachexia by Robin,² or of asphyxia, before the condition is recognized.

CASE REPORT

A 7-week-old male infant was admitted to the Children's Hospital, with a history of difficulty in swallowing and breathing since birth and cyanotic spells for one day.

The infant was born after 8 months' gestation to a 23-year-old primipara. Delivery was normal, and the birth weight was 5 pounds, 12 ounces. At 6 weeks of age the weight was 6 pounds, 6 ounces. It remained stationary during the next week. Because of the difficulty in swallowing, the intake was limited to 1 to 2 ounces of S.M.A. at a feeding. Orange juice and oleum percomorphum had been offered. The mother stated that the baby occasionally arched his back to facilitate the breathing. For two weeks before admission the infant had vomited at least once a day, and the vomiting increased in frequency during the two days before entry.

During this period an upper respiratory infection had increased the nasal obstruction, and in the twenty-four hours before admission several cyanotic spells had occurred.

Examination revealed an acutely ill, malnourished, poorly hydrated infant with noisy respirations, dyspnea, cyanosis, and severe retraction of the sternum on inspiration. There was also considerable nasal obstruction and coryza.

The head measured 14 inches, the chest 12.6 inches, the abdomen 11.3 inches, and the length 21 inches. The cry was hoarse and guttural. The face showed a marked receding chin (see Fig. 1). A left strabismus was present. The ears protruded outward. There was a cleft of the posterior portion of the soft palate and uvula, and the tongue was displaced posteriorly and rested

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against the pharyngeal wall occluding the respiratory passages. The chest was funnel shaped, and breath sounds came through poorly on pulmonary auscultation. The abdominal examination was negative. Neurological examination, except for unsustained ankle clonus, was not remarkable.

Laboratory Findings.—Urine examination was within normal limits. The hemoglobin was 71 per cent; the white blood count was 11,150 with 60 per cent polymorphonuclear leucocytes, 33 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophiles. Blood serum calcium was 10.5 mg. per 100 c.c., and serum inorganic phosphorus was 3.5 mg. per 100 c.c. The Mantoux reaction to 0.01 mg. of old tuberculin was negative. The blood Kahn test was negative.



FIG. 1.—Infant at 8 weeks of age, showing receding chin and sternal retraction.

An x-ray of the chest revealed bilateral emphysema, and the heart was not abnormal.

Course.—The child had a normal temperature throughout his hospital stay, but continued to have cyanotic spells and severe respiratory distress and ate very poorly. He was extremely restless and irritable and required small doses of phenobarbital for sedation.

He was placed in an oxygen tent, fed with a Breck feeder, and given frequent supplemental clyses of 5 per cent dextrose and saline. He was also

given penicillin, 5,000 units every three hours intramuscularly, as a prophylactic against bronchopneumonia. The nose was cleared frequently by suction, and 0.25 per cent neosynephrin nose drops were instilled from time to time. The child frequently assumed the opisthotonic position for relief. It was also noted by the nurses that respirations seemed easier when the infant lay on his stomach.



Fig. 2.—Infant wearing headgear.

The tentative diagnosis on admission was congenital laryngeal defect or web, superior aperture collapse, and upper respiratory infection, and the question of a tracheotomy was seriously considered by the otolaryngologist. Four days after admission, the infant was laryngoscoped and no congenital web or obstruction was found. There was collapse of the structures of the superior aperture. With the laryngoscope in place, it was noted that with the base of the tongue raised, the child could breathe without obstruction or sternal retraction. At this time the correct diagnosis became apparent.

The infant was placed on his abdomen with a small pillow under the upper part of the chest. The cyanosis improved and the respiratory difficulty diminished. The infant was fed in this position from a bottle with the child reaching outward and upward.

A headgear was then devised for the infant with a padded metal bar around the head and padded metal bars at the sides which extended downward and slightly forward; felt pads which impinged between the posterior rami of

the mandible and the external auditory meatus created pressure and pushed the jaw forward as shown in Fig. 2. The headgear was placed on the child eleven days after admission. Wearing the apparatus, the infant's respiration improved and he could be held and fed upright, with substantial increase in the intake of the formula. Thirteen days after admission he was discharged, weighing 7 pounds, 7 ounces, on an evaporated milk formula. Subsequently, the headgear had to be modified with cross tapes across the top of the head to prevent it from riding downward over the ears.



Fig. 3.—Child at one year, showing residual sternal retraction.

The infant wore the apparatus for a month after discharge. He is now one year old, and when seen at monthly intervals was free of cyanosis or respiratory difficulty, despite frequent upper respiratory infections. Feeding has presented some difficulty, with the infant eating poorly and vomiting at times. Weight gain has been slow, but growth and development have been normal. The funnel chest is improving and is less marked (see Fig. 3). At one year the child's height is 29 inches, the weight is 18 pounds, 6 ounces. The head measures 18 inches, the chest 18 inches, and the abdomen $16\frac{1}{2}$ inches. The mandible has grown to some extent but still recedes somewhat.

REVIEW OF LITERATURE

Several case reports have appeared in the literature.³⁻¹¹

Theories advanced to explain the etiology of the development of hypoplasia of the mandible include that of Kiebel and Mall,¹² who attribute it to a

simple arrest of the developmental process. Schwartz⁴ feels that the presence of other associated abnormalities in infancy confirms the theory of Kiebel and Mall. Pierre Robin¹ in his monograph enumerates still other associated clinical manifestations which he feels result from the pre-existing glossoptosis and are secondary to the respiratory and swallowing difficulties. These systemic manifestations are protruding ears, kyphosis, scoliosis, genuvalgum, strabismus, adenoids, dental caries, pigeon breasts, flat feet, abdominal ptosis, and cryptorchidism.

In our patient, strabismus, protruding ears, and pigeon breast were present in infancy.

Warkany¹³ suggested that malnutrition of the embryo might be a possible cause, and was able to produce hypoplasia of the mandible, radius, ulna, tibia, and fibula, plus cleft palate and syndactylism in rats on diets deficient in riboflavin.

Davis and Dunn⁵ believe that hypoplasia of the mandible is due to the weight of the fetal body in utero causing marked flexion of the neck with resulting pressure on the mandible from forceful contact with the fetus's sternum. If this occurs early enough before the mandible is calcified, the deformity is enhanced. Pressure has also been thought to be a factor in the production of the cleft palate.

The genioglossi muscles are responsible for drawing the tongue forward, since their insertion is on the symphysis menti of the lower jaw. With hypoplasia of the jaw and backward displacement of the mandible, the traction of the genioglossi cannot prevent the tongue from dropping backward, and obstruction of the superior aperture occurs.

TREATMENT

It is evident that the cause of the attacks of cyanosis and of the respiratory and feeding difficulties is on a mechanical basis due to glossoptosis. When the head is extended, respiration is facilitated and the jaw is brought forward. Immediate therapy should consist of oxygen; the child's face should be placed down in the prone position with the chest elevated by a small pillow, and the infant should be encouraged to nurse reaching outward and upward, like the young of the lower animals. Robin¹ calls this orthostatic nursing. After and during feeding, Robin² also advises holding the infant erect, without shaking, for ten minutes until the air is expelled orally.

Subsequent treatment for our patient consisted of the construction of a headgear, as first recommended by Eley and Farber⁵ and later modified by Llewellyn and Biggs.¹⁴

Llewellyn and Biggs¹⁴ feel that the mandible eventually grows to normal proportions equalling the growth of the maxilla, in all cases except where there is ankylosis present with atrophy of the genioglossi muscles. The treatment should, therefore, be directed toward artificial means of keeping the jaw forward until adequate muscle action and development has been established. The length of time for wearing the brace depends probably on the time it takes for the infant to overcome the glossoptosis. In our patient, it was one month.

Callister,¹⁵ however, reported a case in which he had no success with the head brace. He employed skeletal tractions of the mandible with good results. Davis and Dunn⁸ used a curved metal form made to fit the upper lip and connected to the nursing bottle through an easily adjustable attachment which permitted lengthening the distance between the nipple and the infant's mouth. This made the infant thrust out its lower jaw in order to grasp the nipple. Babcock¹⁶ described the method by which the temporomandibular structure in front of the external auditory canal is disarticulated, the mandibular heads forced anteriorly, and the gaps filled with costal cartilage.

Hensel¹⁷ performed an osteotomy on the ascending rami of the mandible and then grafted bone into the symphysis menti. These are rather extensive surgical procedures to perform on newborn infants and are reserved for those older children whose mandibles do not develop normally.

TABLE I. REVIEW OF THE LITERATURE ON HYPOPLASIA OF THE MANDIBLE

AUTHOR	AGE	RECED- ING CHIN	GLOS- SO- PTOSIS	CLEFT PALATE	RETRACTION OF XIPHOID	CYANOSIS
Eley and Farber	6 weeks	Yes	Yes	Yes	Shown in photograph but not described	Yes
Eley and Farber	3 days	Yes	Yes	Yes	Inspiratory embarrassment	Yes
Eley and Farber	10 days	Yes	Yes	Yes	Not described	Yes
Eley and Farber	3 days	Yes	Yes	Yes	Inspiratory embarrassment	Died
Schwartz	Newborn	Yes	Yes	Yes	Yes	Respiratory difficulty; died
Lannelongue and Menard	?	Yes	Yes	Yes	Not described	Not described
Lannelongue and Menard	?	Yes	Yes	Yes	Not described	Not described
Lannelongue and Menard	?	Yes	Yes	No	Not described	Not described
Weisengreen and Sorsky	Newborn	Yes	Yes	Not mentioned	Not mentioned	Died
Davis and Dunn	3 weeks	Yes	Yes	Yes	Not mentioned	Yes
LaPage	2 weeks	Yes	Yes	No	Not mentioned	Yes, died
Llewellyn and Biggs	3 weeks	Yes	Yes	Yes	Not mentioned	Yes
Children's Memorial Hospital, Chicago	2 weeks	Yes	Yes	Yes	Suprasternal retraction; inspiratory	Yes
Nisenson	7 weeks	Yes	Yes	Yes	Yes	Yes
Lenstrup	6 weeks	Yes	Yes	Yes	Inspiratory embarrassment	Yes
Lenstrup	1 week	Yes	Yes	Yes	Contractions of thorax; inspiratory	Yes
Lenstrup	1 week	Yes	Yes	Yes	Yes	No
Shukowsky	Newborn	Yes	Yes	Yes	Inspiratory difficulty	Asphyxia, died
Shukowsky	Newborn	Yes	Yes	No	Inspiratory difficulty	Yes
Totals, 19 Cases		19	19	15	7—Inspiratory embarrassment 4—Xiphoid retraction	11

DISCUSSION

Pierre Robin¹ first described the mechanical effects of ptosis of the tongue in his monograph. From subsequent papers which appeared in the literature, it is evident that a definite combination of physical findings are present (see Table I).

Nineteen cases have been reviewed and charted. All of these patients showed deficient development of the lower jaw and glossoptosis. Fifteen had an associated cleft palate. In four there was sternal retraction. In seven others there was inspiratory embarrassment. In the others, nothing is mentioned about the presence or absence of sternal retraction. Eleven had cyanotic attacks.

It is apparent that the presence of receding chin, glossoptosis, cleft palate, and sternal retraction constitutes a clinical syndrome.

SUMMARY

1. A case of hypoplasia of the mandible and glossoptosis, associated with cleft palate and inspiratory retraction of the xiphoid process, is presented.
2. Associated clinical findings are cyanosis, respiratory embarrassment, difficulty in swallowing, and malnutrition.
3. Treatment is primarily postural with the infant placed prone, a pillow under the upper thorax, and the child fed on its stomach with the head extended.
4. The use of a headgear is advocated, devised to keep the mandible forward.

The writer wishes to express his appreciation of the valuable assistance received from Dr. Elvira Goettsch.

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Case Reports

CANDIDA ALBICANS INFECTION IN A CHILD

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THE reports of fungus infection in the literature before 1930 have little meaning as a result of faulty identification of the organisms. In the last decade the peculiarities of fungi have become better known, and mycotic infections have been increasingly reported. Infections of all systems have been described, but rarely for the urinary tract. These have been reported by Oomen,¹ Wessler, C. S.,² and Moulder³ with good biological proof.

CASE REPORT

History.—A female infant, 7 months of age, was admitted Oct. 14, 1946, with the complaint of passing blood per anum. This was associated with colicky pain and a foamy diarrhea. Hematuria had not occurred. Aside from oral thrush a few weeks previously the infant had not been ill. The family history was irrelevant.

Clinical Examination.—On admission the weight was 6 kg. The infant was restless and vomited. The mucous membrane of the mouth and throat appeared normal. The skin was pale, and scattered over the body were erythematous-squamous plaques varying in size from a dot to a centimeter in diameter. The heart and lungs were negative. The abdomen was not distended but was painful to palpation. Peristalsis was visible. Blood was discharging from the rectum, and the anal sphincter was lax. Dark clots followed digital examination. The vulva was covered by a white membrane, and the mucous membrane was inflamed. There was no vaginal discharge.

Entry Laboratory Findings.—The blood count showed 3,500,000 red blood cells, 70 per cent hemoglobin, 15,000 white blood cells, and 320,000 thrombocytes. A differential count showed 1 eosinophile, 6 stab cells, 44 segmented cells, 41 lymphocytes, and 1 mononuclear cell. Bleeding, coagulation, and prothrombin times were within normal limits.

Hospital Course and Subsequent Laboratory Data.—As the signs suggested intestinal obstruction, a surgical consultation was held, and an exploratory laparotomy was done on the day following admission. No abnormality of the intestine was found. After a rather stormy postoperative course with continuous intravenous infusion for four days of casein-hydrolysis and glucose and nothing by mouth, the hemorrhage and diarrhea stopped. The temperature was remittent up to 39° C. and was not affected by 100,000 units of penicillin daily. During this time the urine showed no abnormalities except a few leucocytes.

As there was seemingly pain and tenderness on pressure over the mastoids, an opening of the mastoid was made but no hidden infection was found. The temperature finally became normal although penicillin had been stopped several days previously.

On October 27, yeast cells grew out on a glucose agar culture of a catheterized specimen of urine, and the urinary sediment showed macroscopic white masses, which proved to be collections of mycelial threads showing blastospores and enmeshed leucocytes (Fig. 1). Subsequent cultures proved to be solely

C. albicans (Robin-Berkhout, 1923). The identification was made by the Yeast Division of the Centraal Bureau Voor Schimmelcultures at Delft, Holland, Prof. Dr. Kluyver the director.

Urinary tract examination:

Urine: The pH reaction was 5.8; the specific gravity was 102.5; there was a trace of albumin and no sugar. Sediment showed masses of mycelia. Leucocytes were present in clumps, and there were a few red cells. There were no casts. Cultures for bacteria were negative.

Renal function: Renal function appeared to be good (Rowntree 63.5 per cent). Urea and chloride in the blood serum were normal.



FIG. 1.—Mycelial threads showing blastospores and enmeshed leucocytes.

Cystoscopy: The bladder capacity was normal, as was the mucous membrane, except near the orifice of the left ureter, where small, ivory-white lines were seen. The orifices were not patent. Catheterization of the left ureter was easy, and 5 c.c. of cloudy urine was obtained, showing a trace of albumin, 4 leucocytes per high-power field, and a few red cells. There were no bacteria. The centrifuged sediment showed fungi which grew out on culture as *C. albicans*. A retrograde pyelogram showed a dilatation of the left ureter (Fig. 2) with no abnormality on the right side.

Proctoscopy: Proctoscopy showed a red and swollen mucous membrane for the first 6 cm. In the rectal ampulla were marble-sized white masses considerably obstructing the lumen of the bowel. Removal of these masses caused brisk hemorrhage. There were found to be masses of packed mycelial threads of *C. albicans*.

Skin: Cultures from the skin lesions were negative.

Lungs: Monthly roentgenograms showed a gradually increasing density in the right middle and lower lobes and left upper lobe. The hilar shadow was broadened. No calcified foci were present. Mucoïd material from the

tracheal bifurcation was obtained, which, on smear, revealed branching yeast cells. Although great care was taken, it is not absolutely certain that there was no oral contamination. Cultures from the material were negative.

Other examinations: Fasting stomach contents were free from tubercle bacilli, and guinea pig inoculations were negative. The Mantoux reaction was repeatedly negative



Fig. 2.—Retrograde pyelogram showing dilatation of the left ureter.

Blood vitamin A content was 8.3 I.E. and 17 gamma carotene per 10 c.c.

Roentgenograms of wrists and fingers showed no abnormalities.

The Wassermann and Meinicke reactions were negative. Complement fixation tests for typhoid, paratyphoid, *Bacillus abortus*, and *Spirochaeta icterohaemorrhagiae* were negative. The blood cultures were repeatedly negative.

Course of Disease and Treatment.—A month after admission the child improved spontaneously. Yeast cells in urine and feces decreased in number. This improvement started before the child received large doses of potassium iodide with Cibazol. (Later it was brought to our notice that yeast produces large quantities of para-aminobenzoic acid so that Cibazol was useless.)

A fortnight after cessation of this treatment the urine was free of yeast and the skin clear for the first time. Another fortnight and the feces were also free of yeast.

A diet containing carbohydrate in the form of lactose exclusively had been given in an effort to free the alimentary tract of *C. albicans*, as these organisms do not ferment lactose (Buchanan⁴). The urine was made alkaline with sodium bicarbonate.

Because yeast infection of the lung was feared,^{5, 6} serum of rabbits immunized with *C. albicans* was administered, but the serum caused such severe reactions that it was abandoned.⁷

Special Skin Tests Performed.—Table I shows the skin tests performed.

Scarification reactions were positive only with yeast cell suspensions, and as the child improved these reactions became negative. Intracutaneous injection with living cells and with extracts were positive and gave on repetition a shortened reaction time. No atopic (Hopkins⁷) or anaphylactic reactions were seen. There were neither general reactions nor reaction at previous injection sites. No cross reactions with other fungi or yeasts could be elicited, not even with species of the *Candida* genus. The skin reactions in the control children were negative.

The yeast isolated from the patient was investigated as follows:

1. A series of cultures was treated with x-ray doses of 100, 250, 500, 1,000, 2,000, and 4,000 R. without affecting the growth rate (Jacobson⁹).
2. Anaerobic and aerobic cultures grew equally well.
3. A rabbit weighing 1.75 kg. was injected intravenously with 0.5 c.c. of living yeast cell suspension of 2×10^6 organisms per cubic centimeter. The animal died two days afterwards. Autopsy revealed multiple metastatic abscesses in all organs. Blood culture was positive. Microscopic examination of the abscess content showed branching yeast cells with surrounding mononuclear cell infiltration. No central necrosis or giant cells were seen. These findings are those of "first-degree virulence," according to Mackinnon,¹⁰ who investigated the pathogenicity of *C. albicans*. (See also McKinney.¹¹)

Another rabbit weighing 2.5 kg. had a similar suspension injected into its right ureter, which had been ligated below the injection site. After fourteen days the rabbit, apparently in good health, was killed. Autopsy showed the right kidney to be pale and swollen. Yeast cells and inflammatory reactions could not definitely be demonstrated. The liver showed some foci of mononuclear infiltration. The blood culture was negative.

In summary, intravenous injection of yeast organisms caused septicemia with miliary dissemination of yeast cells, which were recoverable from the multiple abscesses. Kidney infection by ureteral injection was not successful.

DISCUSSION

The question arises as to whether this was a primary infection with *C. albicans*, or whether, as in some reported cases, the occurrence of the yeast was a secondary invasion. The excessive growth of the organism in the intestine, the allergic reactions, and the proved pathogenicity of the strain argue for an infection by the organism.

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Other examinations: Fasting stomach contents were free from tubercle bacilli, and guinea pig inoculations were negative. The Mantoux reaction was repeatedly negative.



Fig 2—Retrograde pyelogram showing dilatation of the left ureter

Blood vitamin A content was 83 I.E. and 17 gamma carotene per 10 c.c. Roentgenograms of wrists and fingers showed no abnormalities.

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TABLE I SKIN REACTIONS

NO AND DATE OF TEST	PREPARATION USED	ORIGIN OF MATERIAL	METHOD OF APPLICATION	RESULT	CONTROLS
A. 12/13, 12/17, 1946	Extract I*	2 day old culture of strain found in patient	Scarification	Negative	Two normal children reacted negatively.
B. 12/14, 12/18	Living yeast cells in suspension	2 day old culture of strain found in patient	Scarification	After 24 hr., a round, raised wheal	Two normal children reacted negatively.
C. 12/15, 12/20,	Living yeast cells in suspension	2 day old culture of strain found in patient	Intracutaneous injection	After 24 hr, a pustula 5 cm. in diameter with central necrotic area and dark red rim	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative
D. 2/19, 1947	Living yeast cells in suspension	2 day old culture of strain found in patient	Scarification	Became negative	Two normal children reacted negatively.
E. 2/15, 2/19	Extract I*	2 day old culture of strain found in patient	Intracutaneous injection	After 6 hr. definitely positive	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative.
F. 3/7, 3/10	Extract I*	Culture of 4 other yeasts†	Scarification	Negative	Two normal children reacted negatively.
G. 3/13	Extract I* (stronger than previously)	Culture of 4 other yeasts†	Scarification	Negative	Two normal children reacted negatively.
H. 3/24, 3/28	Extract I*	Culture of 3 yeasts‡	Scarification	Negative	Two normal children reacted negatively.
I. 5/11, 5/14	Extract I*	Culture of 4 other yeasts†	Intracutaneous injection	Negative	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative.
J. 6/2	Living yeast cells in suspension	2 day old culture of strain found in patient	Scarification	Negative	Two normal children reacted negatively.

*Extract was prepared from actively dividing young cells according to Henderson. A colony of the culture was suspended in 5 c.c. normal saline plus 1 c.c. N/10 hydrochloric acid, boiled for ten minutes, centrifuged, and the supernatant fluid used after neutralization.

†The yeasts used were *C. parapsilosis* (Ashford—Langeron and Talice), *C. krusei* (A Castellani—Berkhout), *Torulopsis neoformans* (Sanfelice—Radaelli), *Saccharomyces cerevisiae* (Hansen).

‡The fungi used were *Histoplasma capsulatum* (Darling), *Actinomyces inornatus* (Baldacci), and *Sporotrichum Beurmanni* (Matruch and Raymond).

From the studies of Owen¹² and others it is probable that infection with a yeast occurs only after sensitization, which can follow repeated invasions of a minor nature. The erythematous skin lesions, which disappeared as the urine cleared, we interpret as a proof of sensitization. The scarification reactions, which became negative when the rash disappeared, also argue for an allergic state. The second and third intracutaneous injections reacted positively in shorter time, which argues for the formation of antibodies after the first injection.

SUMMARY

A case of generalized infection by the yeast *C. albicans* has been described, with localized infection of the left ureter, the bladder, the urethra, and the vulva. Infection of the lower bowel was also present, with symptoms resembling intussusception. At the same time, the lungs were abnormal, possibly due to an allergic reaction. Further arguments for this allergic state were found in the skin rash which was recognized as moniliid, and in the results of the skin reactions to antigen prepared in various ways (Table I). Animal inoculation showed the yeast organism to be pathogenic. Recovery was apparently spontaneous although several therapeutic measures were employed, including potassium iodide, a lactose diet, and alkalinization of the urine.

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TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN

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BECAUSE the use of streptomycin in tuberculosis is still in the experimental stage, we believe it will be of value to report in detail a case of tuberculous meningitis in a 7-year-old boy successfully treated with streptomycin and followed for one year.

Tuberculous meningitis has been described as the most frequent and the most hopeless type of meningitis occurring in infancy and childhood.¹ Approximately 65 per cent of children who succumb to tuberculosis die from tuberculous meningitis, and 90 per cent of cases of this disease occur in the first decade of life.²⁻⁶

Although prognosis is very poor, there are several cases reported in the literature in which the patients have recovered without the use of specific treatment. In 1931 Kramer and Stein⁷ selected seventy-three cases which they considered to be authentic in a review of the literature. Cases of recovery since then have been reported by Jennings,⁸ McQuinness,⁹ Kelly,¹⁰ Hobson,¹¹ and Parry.¹² Experience at Boston City Hospital over the past thirty-two years reveals uniform fatal termination in all cases of tuberculous meningitis. There have been 178 deaths in children, and all died on the average within seven days after admission to the hospital.

CASE REPORT

The patient, a 7-year-old boy, was admitted on Oct. 24, 1946, because of cough, fever, anorexia, and irritability of two weeks' duration. Approximately two years prior to entering Boston City Hospital he was treated at St. Elizabeth's Hospital in Brighton for tuberculous pleurisy with effusion involving the left lung. He remained in the hospital for two weeks and was then allowed to continue with bed rest and supportive therapy at home. There was no other previous serious illness.

On the day of admission the patient appeared irritable and listless, and his mother noted for the first time a weakness in the left arm. When seen by the family physician he was found to have nuchal rigidity, and admission was advised with the tentative diagnosis of tuberculous meningitis.

Examination of the patient revealed a somewhat poorly nourished child. He appeared drowsy most of the time but was cooperative and well orientated. Besides the nuchal rigidity, there was a bilaterally positive Kernig's sign, a left facial weakness, and a paresis of the left arm and leg.

The temperature was 103° F., the pulse 100, and the respirations 20. The blood pressure was 100 systolic, 80 diastolic.

Examination of the blood revealed a red cell count of 4,500,000 with a hemoglobin of 80 per cent, and a white cell count of 15,700, the differential count being 46 per cent neutrophils, 50 per cent lymphocytes, and 4 per cent monocytes. The urine gave a positive test for albumin and contained 10 to 20 red blood cells per high-power field. The spinal fluid on admission showed a normal pressure and had the appearance of ground glass, with 79 neutrophils and 137 lymphocytes per cubic millimeter. The total protein was 51 mg. per cent, sugar 25 mg. per cent, and chlorides 617 mg. per cent. No pellicle formed on standing, and no acid-fast bacilli could be seen on smear. However, a guinea pig inoculation at this time was reported as positive for tuberculosis six weeks later. Chest x-rays revealed hila thickening and increased lung markings with a linear strand of thickened pleura at the right base. The Mantoux test was positive with 0.01 mg. of tuberculin.

Although a diagnosis of tuberculous meningitis was made, no streptomycin was immediately available. Penicillin and sulfadiazine were administered prophylactically, but there was no fall in the temperature. On Nov. 1, 1946, the ninth hospital day and twenty-third day of illness, streptomycin therapy was started.

The patient was treated with streptomycin for a period of 141 days (almost five months), receiving a total of 70,458,332 units intramuscularly and 2,675,000 units intrathecally. At first, 83,333 units were given every four hours intramuscularly (0.5 Gm. daily) for forty-seven days. The dosage was then changed to 125,000 units every six hours (0.5 Gm. daily) for the patient's comfort, and was continued until the end of treatment. Intrathecally, he received 25,000 units daily for the first forty-three days, then 50,000 units every other day for seventeen days, and finally during the last eighty-two days he received 50,000 units twice a week.

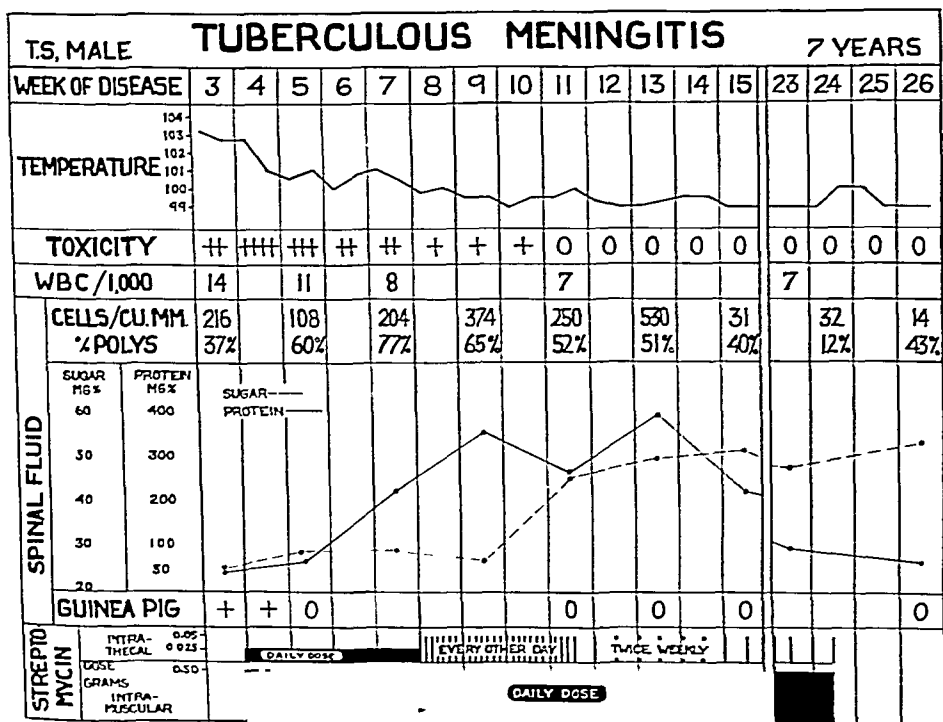


Fig. 1.

Following admission the patient's temperature remained between 102° and 103° F., but shortly after streptomycin therapy was instituted the temperature gradually began to fall, ranging between 99° and 102° F. After approximately three months of treatment his temperature remained normal. There was a daily rise to 100° F. for four days following cessation of treatment, although no cause could be found for this.

During the first three days of hospitalization the patient ate well and seemed to be fairly well orientated. His speech was somewhat incoherent, he was incontinent of urine and feces, and he slept much of the time. Gradually the patient began to fail, however, and by the tenth hospital day he had become

disorientated, extremely drowsy, and was unable to speak. When aroused he could be fed and would answer questions by nodding, but did not recognize members of his family. Although streptomycin therapy was instituted at this time, he did not struggle or cry when receiving the intramuscular injections or daily lumbar punctures. By the third week of treatment he began to use his right hand in feeding, appeared interested in his surroundings, and cried when the lumbar punctures were performed. On November 23 he spoke a few words for the first time in three weeks. Guinea pig inoculations of spinal fluid at this time were negative and remained so throughout the hospital course. Following this the patient slowly became more responsive and orientated. During his seventh week of hospitalization he responded to simple commands, could repeat words after the examiner, and could identify a few simple objects. There was no improvement in the left facial paralysis, and splinting and physiotherapy were required to prevent contracture deformities of the left arm and leg. Gradually the mental status improved, and by the ninth hospital week he seemed to be as bright and alert as any normal 7-year-old boy.

The spinal fluid sugar slowly rose to normal, as shown in Fig. 1. Between the eighth and thirteenth weeks there was an increase in the cells and a marked rise in total protein, and this may have represented a reaction to the streptomycin. Chest x-ray on December 5 revealed a hazy density in the right hila region, but by Feb. 12, 1947, the lung fields were completely normal.

During the last few weeks of treatment, physiotherapy was continued and gradual mobilization attempted. He was unable to use his left leg until the fifteenth week of treatment, and then only with the aid of a posterior splint. At the time of discharge he could walk quite well with the leg splinted, and although the left arm could be fully flexed and extended he could not grasp objects with his hand. A Stanford-Binet psychometric test administered shortly prior to discharge revealed an I. Q. of 105 and the level of intelligence was concluded to be "good average."

The patient was discharged on April 2, 1947. During the first few weeks at home he tended to stagger when walking. At present, one year from the onset of illness, he appears clinically well except for the persistence of his left facial weakness and left hemiparesis. The arm can be used, but the child is still unable to grasp with the fingers. The left leg drags slightly and has a "slapping" characteristic when walking or running. He has remained mentally alert and active, but at times is very irritable and restless. There has been no impairment of vision or hearing.

DISCUSSION

Although the boy whose case we have presented appears to be cured clinically, it cannot be stated with certainty that the tubercle bacilli have been completely eradicated.

The fact that streptomycin is the most effective antibacterial agent known for tuberculosis has been shown through experiments conducted by Hinshaw and Feldman and their co-workers.¹³⁻¹⁶ Guinea pigs infected with virulent tubercle bacilli were treated with streptomycin. Although death was prevented, the action seemed to be suppressive rather than sterilizing, as tubercle bacilli were recovered from the spleen in a high percentage of cases. Hinshaw, Feldman, and their co-workers state that "streptomycin is most valuable in cases in which temporary suppression of the infection will enable the patient to gain the ascendancy over his disease; healing then occurs by natural processes," and believe that streptomycin is indicated in the treatment of miliary tuberculosis and tuberculous meningitis.¹³

Recent cases of miliary tuberculosis in children treated and cured with streptomycin have been reported by Colby and Goettsch¹⁷ and Sanford and O'Brien.¹⁸

The first detailed report on the use of streptomycin in tuberculous meningitis was by Cooke and associates¹⁹ in the treatment of a one-year-old infant. A total of 15,049,000 units intramuscularly and 4,951,000 units intrathecally were administered over a period of sixty-eight days. At the time of writing the child was clinically well except for bilateral deafness and occasional periods of vomiting. Krafchik²⁰ has reported a case of a 15-month-old boy treated with streptomycin for fifty-seven days who obtained complete clinical recovery. He received a total of 24,000,000 units intramuscularly and 2,800,000 units intrathecally. Hinshaw and co-workers,¹⁶ in their summary of 100 cases of tuberculosis in which the patients were treated with streptomycin, report on the results in nine cases of miliary tuberculosis and tuberculous meningitis. Of the four surviving patients only one was clinically well and asymptomatic. Reactivation of the disease had occurred in one, and residual neurological disturbances were present in the other three patients, including blindness and profound disturbances of cerebellar function. Treatment consisted of 100,000 to 200,000 units of streptomycin intrathecally daily for two to six weeks, and daily intramuscular injections of 2 to 3 million units for six months. None of the patients who died had received intrathecal therapy, and none of those who received intrathecal therapy had died. Other cases have recently been reported by Applebaum and Halkin,²¹ and Mehas and Truax.²²

In addition to the case reported here we have since used streptomycin in the treatment of four other children with tuberculous meningitis, two of whom are still living. One patient, a 2-year-old boy, was comatose on admission. Although he did not appear to improve with treatment he remained alive for eighteen days. The other patient who died was a one-year-old boy who had an associated miliary tuberculosis and died on the thirty-first day of treatment. The third patient is a 16-month-old girl who clinically and bacteriologically has recovered from tuberculosis, but is now partially blind and has marked cerebellar dysfunction. The most recent case is that of a 3-year-old Negro girl who has been discharged after 107 days of treatment and is clinically well except for a very slight right facial weakness. She received a total of 77,244,000 units of streptomycin intramuscularly and 1,625,000 units intrathecally.

SUMMARY

1. The case of a 7-year-old boy with tuberculous meningitis who has apparently been successfully treated with streptomycin is reported.

2. The reported cases of tuberculous meningitis treated with streptomycin have been reviewed.

3. Although results are variable, it is felt that early and intensive use of streptomycin intramuscularly and intrathecally may well favorably modify the course of tuberculous meningitis.

The authors wish to express their appreciation for the valuable assistance received from Dr. Thomas F. Paine in the treatment of the patient and the presentation of this paper.

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ADDENDUM

Since the writing of this paper, the 16-month-old baby and the 3-year-old Negro girl have both died. The former, who was clinically cured of the meningitis although cerebral damage was present, died following a gradual downhill course. Death occurred exactly thirteen months after admission, and an autopsy could not be obtained.

The 3-year-old girl, who was apparently almost completely cured, died just nine months after her first admission. She was well until two days before death, when she suddenly convulsed, became comatose, and developed a left hemiparesis. Autopsy revealed that death was due to a thrombosis of the right middle cerebral artery, which was surrounded by a large tuberculoma. This had caused infarctions in the right frontal and right parietal lobes. There was also an old infarct of the left internal capsule and putamen. Scattered tubercles were found in the mediastinal glands, liver, and spleen, from which acid-fast bacilli were found on smear.

TIME ELEMENT IN THE DEVELOPMENT OF IRREVERSIBLE BRONCHIECTASIS

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It is generally known that bronchiectasis may be the result of infection behind a partial obstruction in a bronchus. As a result of the suppurative lobular pneumonia, the bronchial wall becomes necrotic with the eventual destruction of the musculoelastic coat. It has been thought that up to a certain point this pathologic process is reversible; for example, early relief of the obstruction to permit free drainage will allow the inflamed bronchus that is not as yet significantly damaged to heal with the restoration of practically normal bronchial structure. The point at which the process becomes irreversible and at which bronchiectasis is established is thought to be the time when a significant amount of necrosis has taken place in the musculoelastic coat of the bronchus or bronchiolus. There are only a few recorded cases in which an accurate determination can be made as to the length of this time.

Erb,¹ in his detailed report on "The Pathogenesis of Bronchiectasis," describes a case in which a 6-year-old girl died three weeks following aspiration of a tooth into a bronchus. Post-mortem examination at that early date revealed dilated bronchi with varying degrees of destruction of the musculoelastic coat. At that time there was no granulation tissue present. He also recorded a few cases in which the duration of time from the approximate onset of the infection to the time of death varied from four to six weeks. Erb divided the development of bronchiectasis into two periods—the stage of destruction, occurring in the first six weeks of infection, and the stage of repair, after six weeks had elapsed. The point at which the process becomes irreversible and bronchiectasis is established is thought to be the time when necrosis is found completely through the musculoelastic coat. The length of this time is influenced by many factors, such as the severity of infection, the degree of obstruction, the resistance of the patient and the virulence and number of organisms.

Because there are so few cases recorded in which it is possible to determine accurately the time of the onset of the infection, and because of the view held by some that bronchiectasis once established may be reversed, we are reporting a case in which there was a lapse of seven weeks from the onset of the obstruction until lobectomy demonstrated a well-developed and irreversible bronchiectasis.

CASE REPORT

C. B., a white boy 5 years old, was admitted to the Children's Surgical Service, Bellevue Hospital, May 23, 1944, having been referred because of a foreign body (screw) in the right lung. His past history was irrelevant. He had never had any respiratory infection of consequence nor any other illness of importance. Until the onset of his present disability, he had been a normal, active, and healthy child.

On April 12, 1944, he aspirated a small screw which lodged in the right main bronchus. His mother realized immediately what had happened and took him without delay to a hospital in the vicinity of his home. Roentgen examination at this institution showed the screw in his right lung, and bronchoscopy was performed promptly.

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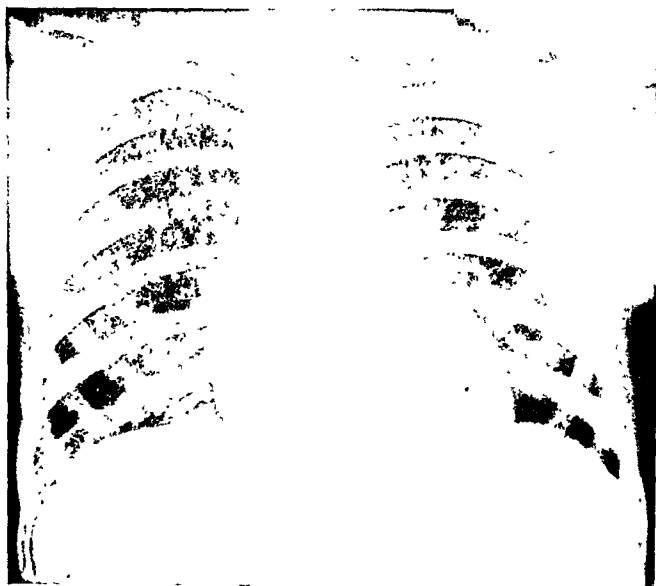


Fig. 1.



Fig. 2.

Figs. 1 and 2.—Posteroanterior and lateral roentgenograms showing location of screw.

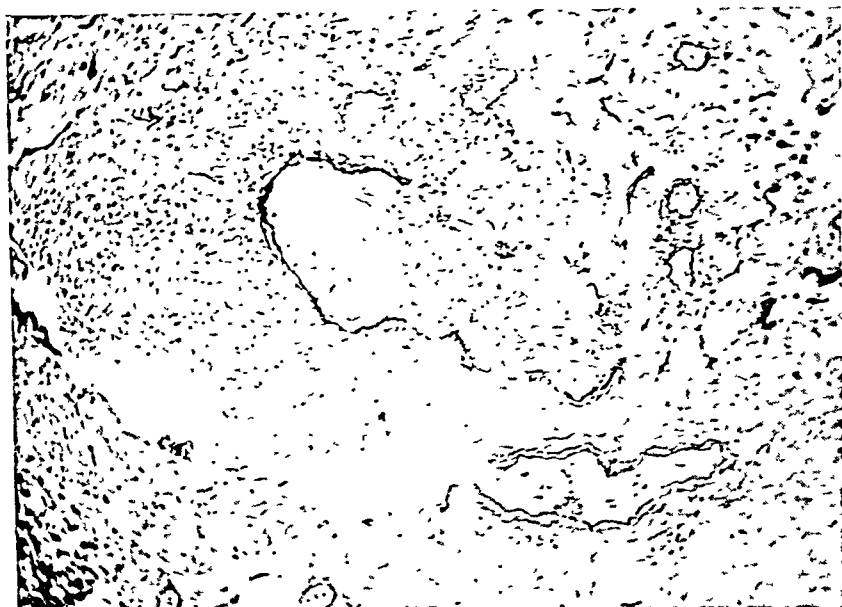


Fig. 3.—Photomicrograph X150. Elastic and connective tissue stains showing disrupted and partially fragmented elastic tissue in wall of inflamed bronchiolus.

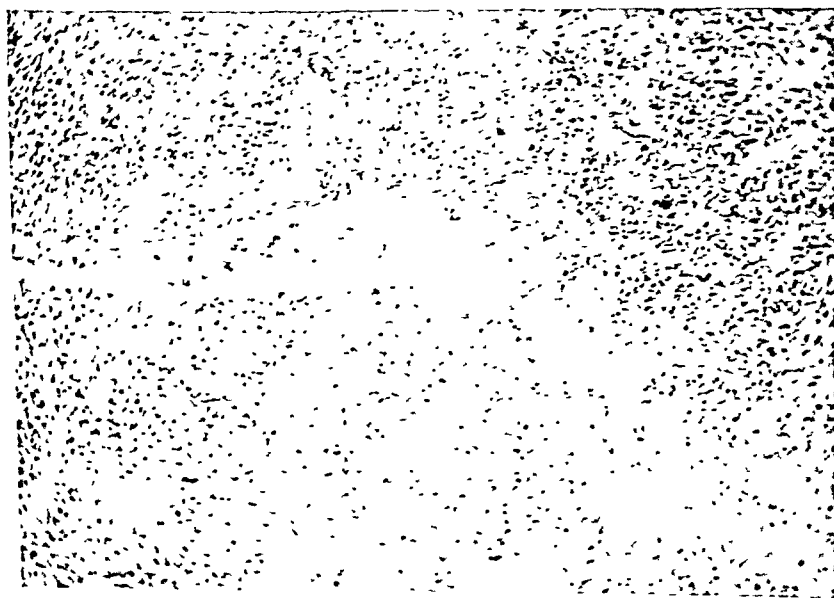


Fig. 4.—Photomicrograph X150. Elastic and connective tissue stain showing complete absence of elastic tissue and complete necrosis of bronchiolar wall.

The screw was visualized in the right main bronchus, but attempts to remove it were unsuccessful. On the two successive days two more attempts were made, but they served only to wedge the screw tightly in the lower lobe bronchus from which it could not be extracted. Following the last attempt, severe respiratory obstruction developed, necessitating tracheotomy. This procedure relieved the obstruction, and in due course the tracheotomy tube was removed and the wound healed. Meanwhile, a cough developed which was productive of a small amount of mucus.

Upon admission to Bellevue Hospital, physical examination showed a well-nourished and developed boy of 5 years. He was coughing constantly and raising a moderate amount of whitish sputum but no blood. He was active and did not appear ill. Except for his lungs and the tracheotomy scar, no abnormalities were disclosed. Moderate dullness could be elicited over the base of the right lung, and a few coarse bubbling râles could be heard in this area. Roentgen examination showed a screw about 1.5 cm. in length in the right lower lung field (Figs. 1 and 2).

Lobectomy was performed June 2, 1944, fifty-one days after aspiration of the foreign body. The right sixth rib was resected and the seventh rib transected at its neck. The pleural cavity was entered through the bed of the sixth rib. The lower lobe was free and easily delivered, but the foreign body could not be palpated. The lobe was removed by the individual ligation technique and after removal was opened to demonstrate the foreign body. The wound was then closed to the emergence of a drain inserted through the resected sixth rib.

Convalescence was complicated by the development of empyema, from which *Streptococcus hemolyticus* was cultured. Sulfadiazine could not control the infection, and eventually the sinus tract had to be reopened. Bronchopleural fistula was never demonstrated, and later with the aid of penicillin, which had just then become available to us, the wound healed and the patient was discharged Nov. 18, 1944.

Description of Surgically Removed Lobe.—The pleura was smooth and glistening. The lung was subcrepitant. The site of the screw was indicated by several rust stains. The screw apparently had been embedded in the bronchus supplying the lower segment of the lobe. This segment was less crepitant than the remainder of the lobe. The bronchi in this segment were definitely dilated and in some instances were two to three times the normal caliber. Patchy areas of consolidation were present in the parenchyma surrounding these bronchi. The bronchial mucosa of the involved segment was reddened, granular, and ulcerated. The remainder of the lobe had a congested appearance; the bronchi and bronchioles were of normal caliber.

Histologic examination of sections through the involved segment revealed varying degrees of destruction of the bronchi and bronchioles. This destruction ranged from mild involvement of the mucosa and musculoelastic layer to complete necrosis. At some points there was beginning granulation tissue proliferation into the wall of the bronchi. In some areas inflammatory exudate in the alveoli was also undergoing organization. Elastic and connective tissue stain revealed that the elastic layer in places was completely destroyed and in other places partially fragmented (Figs. 3 and 4). This was also true of the muscle.

DISCUSSION

The early gross and histologic changes in the development of bronchiectasis have been adequately described by Erb.¹ Of interest, however, is the unusual degree of permanent damage to a large number of bronchi and bronchioles which developed in our patient in a period of such short duration as seven weeks. The fact that this process was present to such a degree is of even greater interest

when one realizes the patient was relatively symptom-free except for a cough during this period.

Fleischner² reported a case in which he claims the bronchiectasis was reversed to normal after being established for seven months. In view of Erb's detailed description and the findings in the case we have just reported, it seems unlikely that such an event could take place. The development of bronchiectasis is dependent to a great extent upon the destruction of the musculoelastic layer. Whether or not this destruction begins as a gradual ulceration through the mucosa or as a diffuse inflammatory process of the bronchial wall, is immaterial. The fact remains that once the elastic layer is destroyed, it is replaced permanently by fibrous tissue and can never be restored to normal. This process takes place within a rather short period of time. Thus it seems from a time basis and an anatomic basis that once bronchiectasis is established, the bronchial wall cannot be restored to normal.

SUMMARY

A case is presented in which the time for the development of bronchiectasis could be accurately estimated.

A study of this case indicates that the early destruction of the musculoelastic layer precludes the possibility of a reversibility of bronchiectasis.

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HOMOLOGOUS SERUM HEPATITIS

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THE improved availability of prepared plasma to the practitioner plus the fact that its usage does not require blood typing or crossmatching has increased its popularity as a therapeutic agent. Because plasma is being used more freely, the hazard of its causing homologous serum hepatitis must not be overlooked.

Homologous serum hepatitis became a real problem to the armed services during the recent war and has received considerable attention and investigation. Whenever pooled blood, serum or plasma, is given parenterally there is the chance that it contains an agent, thought at present to be a virus,¹ which will cause hepatitis with or without jaundice. The severity of the hepatitis is not related to the size, route, or frequency of the injection.² Therefore, every time a parenteral injection of plasma or whole blood is given there is the risk of giving to the patient a potentially fatal infection in a definite percentage of cases.³ The liver cells die from a coagulation necrosis.¹

To help prevent such fatal potentialities it is recommended that no blood be taken from any donor who has received blood or plasma within the previous six months or who has had any so-called virus infection during that period of time. The incubation period of homologous serum hepatitis is from two to five months.⁴⁻⁷

The following is a case report of homologous serum hepatitis with encephalitis and anuria in a 3-year-old child subsequent to the intravenous injection of plasma.

On June 5, 1946, C. H. was in an automobile accident and sustained a compound, comminuted fracture of the right leg. He was immediately admitted to James Walker Hospital. On June 8 an open reduction was done and a metal plate was inserted. The patient went into shock on the operating table and was given 450 c.c. pooled plasma. Later that day he was given 350 c.c. intravenous glucose. He was started on a course of penicillin, 20,000 units every three hours.

On June 11 blood examination revealed: hemoglobin, 40 per cent; red blood cells, 1,820,000; white blood cells, 8,500; and polymorphonuclear cells, 56 per cent. On June 12 he was given 200 c.c. whole blood from his father. For the next seven days he ran a temperature ranging from 99° to 103° F. On June 17 the hemoglobin was 78 per cent; red blood cells, 4,050,000; white blood cells, 9,350; and polymorphonuclear cells, 53 per cent.

On July 8 he was again operated upon. The metal plate had slipped, and there was overriding of the bone ends. Screws were put into the metal plate. On this day and again on the following day he received 200 c.c. whole blood from a friend. Neither the friend nor the father had received blood or plasma or had had any virus infection during the preceding six months.

On August 6 the patient was discharged home in good condition.

On September 9 (three months after the injury and the reception of plasma) he developed a low-grade fever, malaise, and vomiting. At this time he was found to have hemoglobin of 82 per cent and white blood cells, 9,000.

On September 14 the child was admitted to Babies' Hospital with the complaint of fever and vomiting for five days, and jaundice, anuria, and stupor for one day. Stools remained normal in color.

Physical examination revealed a fairly well-developed and nourished white male child aged 3 years, weighing 30 pounds, with generalized moderately jaundiced skin and sclerae. He was stuporous and appeared to be acutely ill. There was no lymphadenopathy. Ears, nose, and throat were negative. The heart had normal rate and rhythm with no murmurs. The lungs were clear. Liver, spleen, and kidneys were not palpable. There was slight nuchal rigidity. Reflexes were physiologic.

Laboratory Findings.—On admission the urine was negative for albumin, sugar, and urobilinogen, the specific gravity was 1.014. Bile (methylene blue test) was positive as was the test for acetone. Urine on the eighth hospital day was negative for bile. Urine culture on the fourth hospital day was sterile. Stool specimens were repeatedly negative for ova and parasites. Spinal fluid on admission was clear with 13 cells per cubic millimeter and with slight increase in globulin. A qualitative van den Bergh test on the second day gave a biphasic direct reaction. Total blood protein on the second day was 5.15 Gm. Blood was Rh-positive, Type A.

TABLE I. BLOOD EXAMINATIONS

HOSPITAL DAY	HEMO-GLOBIN (%)	R.B.C.	W.B.C.	POLY-MORPHONUCLEARS (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	BASOPHILES (%)
Admission	80	4.9	17,800	70	30	2	
2	77	3.7	16,100	50	48	1	1
8	73	3.9	9,800	80	48		
13	88	4.7	10,800				

Hospital Course.—On admission the boy was irrational. He groaned and was very restless and voided involuntarily. The first five days in the hospital he remained stuporous and was given intravenous glucose once or twice daily. Other therapy was symptomatic only.

By the sixth hospital day he was talking coherently, was playful, and able to sit up in bed. On the seventh day his jaundice was noticeably decreased, the liver was palpable two fingerbreadths below the costal margin, and the abdomen was distended. On the ninth day he had a fluid wave, shifting dullness, and pitting edema of the legs.

On the eleventh and twelfth days he received two whole blood transfusions of 200 c.c. each, the friend again being the donor. This treatment was given to correct a fall in the hemoglobin and red blood count.

Throughout his hospital course the boy had an evening rise of temperature to 100°-101.6° F. He was discharged from the hospital on the thirteenth day (September 26) in an improved condition. The jaundice, ascites, and edema disappeared one week after he left the hospital.

With the exception of recurring tonsillitis he has been well since this episode, has gained weight, and has been symptom-free.

SUMMARY

A case report of homologous serum hepatitis in a 3-year-old child which occurred three months after parenteral injection of pooled plasma has been presented. The patient also had encephalitis and anuria as complications of the hepatitis. This case is reported to stress the fatal potentialities of pooled human blood products and the importance of using no donor who has received blood or plasma or has had any so-called virus infection during the preceding six months.

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Medical Care

THE TREATMENT OF COMMON RESPIRATORY INFECTIONS

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THE answers to questions involving the diagnosis and treatment of common respiratory infections in examinations given by the National Board and by the New York State Board of Medical Examiners have suggested this review of the subject. Common colds and their complications comprise the greater part of medical practice, adult as well as pediatric, and it would seem that candidates for licensure should have a reasonable amount of knowledge about the recognition and care of such infections, but this does not seem to be the case. Questions which describe a case of simple acute pharyngitis or tonsillitis are regularly missed by overshooting the mark, and diagnoses of poliomyelitis, diphtheria, meningitis, or almost any more serious disease are made by about three-fourths of the candidates. The answers on treatment are equally absurd. Admitting the patient to a hospital, ordering elaborate diagnostic procedures, laboratory tests, and heroic treatment, seems to be the only plan which occurs to most candidates.

The practicing physician is not free from guilt in this direction. I see many patients in consultation whose parents have been subjected to great and needless expense, as well as to undue anxiety. For example, a child with an acute pharyngitis, or "grippe" with a red throat, is treated with sulfonamides for two or three days. If the fever does not yield promptly, as it often does not, especially when the general care of the child has been neglected, the patient is rushed to the hospital. Penicillin intramuscularly is usually started at once and given every few hours, the pain disturbing the child's rest. Orders are given for complete blood counts and cultures, urinalysis, x-rays of chest, lumbar puncture, throat cultures, etc., etc. The parents eagerly wait the results of the many tests. Before they are all reported the patient is usually convalescent, for the four-day fever has run its normal course, in spite of the treatment! When the hospital bill is rendered, the shock to the parents does not endear the physician to them. The small child is often left in a nervous and unsettled state from being taken out of his familiar home into the hospital, where strangers do painful things to him, mostly unnecessary, and where he is often neglected in essential matters.

For the reasons just given a discussion of the care of colds and their complications seems justified. It cannot cover the diagnosis of all the respiratory infections, but it must be pointed out that simple rhinitis, sinusitis, acute pharyngitis, follicular tonsillitis, otitis, laryngitis, tracheitis, and bronchitis comprise the largest part of acute illness in childhood. One should be able to make a diagnosis of the site of the respiratory infection from a careful analysis of the symptoms and a thorough examination for physical signs, or lack of them.

I have always been annoyed by the blanket diagnosis of "upper respiratory infection," which is applied to *all* acute respiratory disease by students, interns, and practitioners—even when the only physical signs are râles at the base of the lungs.

The treatment of all these conditions may be divided into general and special measures. Every acutely ill child needs care as a sick child, not just as a case of a disease. The patient is often forgotten in ordering drugs or antibiotics, yet the child's recovery depends more on his nursing care than on the drugs given him. It is the physician's duty to instruct the mother or nurse in the simple things which promote the child's comfort, increase resistance, and hasten recovery. Too often he takes the general care and nursing for granted, or perhaps wearies of repeating it to every mother, or omits it because it has never occurred to him that such matters are important to the patient or of concern to the physician.

GENERAL TREATMENT

Rest is needed by every sick child. Freedom from muscular activity, changing temperatures, and nervous strain relieves the vital forces of the body and allows them to be devoted to building up resistance to infection. It is the habit of some physicians to allow children to be up and out of doors with a cold if they have no fever. Mothers are astonished when a child with a cold is ordered to be put to bed when the sun is shining outside. It is my experience that the child who goes out with a little cold too often comes back with a bad one, an otitis, or even a pneumonia. Children who are put to bed promptly at the onset of a cold usually have a milder infection, fewer complications, and a more prompt recovery. Rest, however, does not mean that the child must lie flat in bed with nothing to amuse him. He may sit up in bed, on a couch, or even in a big chair if he is properly dressed and covered. His clothing should be adequate but not too heavy. His legs, which are under the bedding, need only one layer, a nightgown or pajamas. His trunk and arms need somewhat more—either a shirt under his night garment or a light robe or sweater over it. But when he lies down to sleep one layer is sufficient, for a shirt under the night garment, makes him too hot and he is likely to throw off the bedding and then become chilled. The bedding should not be too heavy. I have seen many a child with high fever (104° to 105° F. or more) covered with shirt, night garment, sweater, or bathrobe, and four to five blankets. It has been shown that the temperature of healthy children can be raised several degrees by bundling of this sort. This matter definitely concerns the doctor, and he should not forget it.

The child in bed must be amused. Mothers frequently say: "That child will not stay in bed." Of course he will not lie flat without occupation unless he is too prostrated to hold up his head. A sick child needs more attention in this direction than a well one. First he must be made comfortable with pillows or back rest. A bed table or lap board is of great help because it gives him something to play on, a focus for his attention which helps to keep him quiet. He must have small toys with which he can play on his lap, not large motor vehicles which go on the floor. New toys, books, crayons, sewing—all the endless small occupations which entertain the child—must be provided, a new one

every few minutes in all probability, for the sick child's attention lags easily. A "wonder bag" is an old standby: a large paper bag with many small toys, old and new in it, from which the child can take out one thing at a time. Toys in boxes, one to be opened every hour, may divert him. Play should not be too continuous if fever is present, but broken by rest periods at intervals. Radio music of the softer kind may be quieting, but not loud jazz, and selected programs, not crime features nor exciting soap operas.

The sick room should be kept at a temperature not over 68° to 70° F. Most houses, except those of the better class, are kept too hot. It is not uncommon to find a sick child, overbundled in bed, in a room at 85° to 90° F., the relatives "keeping him good and warm" because he is sick. The mother often is dressed for midsummer, in a cotton dress with bare arms and legs, but the poor little child is sweating in the Turkish bath temperature. The mother must be instructed to keep the room cool and to put on more clothing if she is chilly. Except in the coldest weather, radiators and registers in the sick room should be turned off and the room warmed through open doors. A steam radiator will overheat almost any room if left on longer than a few minutes at a time. The air in these hot rooms is, of course, relatively dry, for the need for moisture in the air rises rapidly with each degree of temperature. If fresh outside air is admitted, it is not always necessary to provide extra moisture. It does no harm to add it to the air, and this may be desirable in some cases. An electric stove with a pan of boiling water, or a wet Turkish towel on the radiator while it is turned on, will evaporate a large amount of water in a short time. The usual small "vaporizer," which holds only a few ounces of water, is a futile gesture, not worth its cost. I am skeptical about the value of steam, medicated or otherwise, in most respiratory diseases. If the room is kept cool and the air fresh, there is usually enough moisture. That fresh air is needed in every sick room almost goes without saying, but the method of supplying it depends on many factors—the season, the outdoor temperature, the direction of the wind, and the position of the bed and windows. In mild seasons windows may be kept wide open, but in winter a small crack may suffice, especially with a windward window. In bitter weather the window may be opened wide for a few minutes every hour or two, the child being covered warmly meanwhile. New air must be supplied effectively. The mother who opens the window a small distance at the top and then covers it with a drawn roller shade is fooling herself but not the open-eyed physician.

Bathing is needed more by the sick child than by the well one. There is usually considerable perspiration in bed, insensible or obvious, due to the fever, antipyretics, and often by overcovering. The fear of bathing during a cold is quite ungrounded. A child may safely have a quick tub, not too warm and *not* in an overheated bathroom, for he may be chilled on returning to a cooler room. Sponge baths are more chilling, more work, and less efficient. Sponging may well be reserved for reducing temperature in hyperpyrexia, although with a small child, who can easily be carried to the bathroom, a lukewarm tub will accomplish the result even better and much more easily.

The planning of treatment of acute illness so as to do all that is necessary, spare the mother's time, and disturb the child as little as possible is something that never enters the head of the general run of physicians. Witness the order sheet for almost any acutely ill patient in any hospital. Temperatures are taken every four hours; nourishment is given at the nurses' convenience; drugs or injections are given every three hours, and nose drops or other treatments every hour or two. I once saw in consultation a child moderately ill with pneumonia who was having thirteen different things done to him at intervals of from one to four hours. Three nurses were kept busy, but the poor little fellow was given no time to sleep! Many such incidents could be cited. The plan of treatment should be laid out with care to avoid such errors. The best plan is to order the mother to do everything which must be done at one time, and then let the child alone to play or rest until the next series of treatments. The traditional four-hour interval is not the best one, for it allows only four feedings in the daytime and it is often desirable to give five. The three-hour interval (7-10-1-4-7) is a better solution, for it gives five feedings and treatments in twelve hours. If necessary, one or more may be given at night. The mother or nurse should go through a definite sequence at each three-hour period. The best one seems to be as follows: Take temperature, feed, give medicine and treatments; then let alone or amuse until three hours have passed. Water may be given during the interval. My associates and I have found useful a printed order sheet for acute illness. It may be modified for individual cases. Exact hours for food, medicine, and treatments are always written. Bathing may be done between temperature-taking and feeding. (See Fig. 1.)

A plan like this makes the care of the patient much easier for the mother. She can plan her day, attend to her duties, or even rest, if the child does, until the next three hours are past. The physician who orders medicines, treatments, food, and temperature taking at all sorts of intervals should be compelled to stay with the patient for twenty-four hours and try to carry out his own orders.

The feeding of the sick child is more easily planned on the three-hour schedule than on any other. This feeding should definitely be prescribed as to quality and quantity as well as intervals. The sick child, especially one with fever, has a diminished digestive capacity, as shown by his anorexia, and by the results if too much food is given, since vomiting often occurs. The hydrochloric acid of the gastric juice is much diminished with the onset of fever. The child, therefore, cannot easily digest certain foods, and chief of these is milk, which is the heartiest food he gets. Large and tough milk curds are often more than the stomach can handle, and are returned more or less promptly in evidence of the fact. Homogenized milk is tolerated but little better. The sick child needs three things: water, carbohydrate, and alkali. He does not need much protein or fat, and vitamins can be disregarded in brief illnesses. Therefore the diet in illness should contain starchy foods—cereal, bread (preferably toasted), sugar (in moderation), and potato. These give him carbohydrates to prevent acidosis. Fruit juices supply alkalis (citric acid yielding bicarbonate), some calories in their sugar, water, and ascorbic acid for good measure. Other liquids may be added, such as broths or vegetable juices for variety. Palatable desserts,

such as cornstarch puddings, gelatin, applesauce, and ice cream, may be given to tempt the child to take calories and carbohydrates. The small amount of milk in some of these will do less harm than milk taken plain, since the curds will be smaller. It is a shock to many students, nurses, and even physicians to learn that a milk diet is not the first thought in illness. Many years ago I was appointed a visiting physician to a hospital for infectious diseases. There were several severe cases of scarlatina with high fever, the children toxic and prostrated and on a pure milk diet. The custom was to give only milk till the fever was gone, then add cereals. When I ordered the sequence reversed, the institution was rocked to its foundations. It must be repeated that the exact kind of food, the amount of it, and the hour at which it is to be given must be written plainly and in full. It is wise to alternate carbohydrate foods with orangeade. As the fever leaves, more milk may be added, and then eggs, meat, and vegetables during convalescence.

The Bowels. A daily evacuation is even more important for the child in sickness than in health. This matter is one which is regularly neglected by the physician, judged by patients seen in consultation and in hospitals. He may order a cathartic or an enema early in an illness, but too often forgets to give further instruction thereafter. A day or two with no bowel movement results in higher fever, more anorexia, a coated tongue, bad breath, and delayed recovery. The child who is seen at the onset of an illness should have an enema at once, unless the mother is sure that there has been an adequate evacuation that day. A soapsuds enema is the quickest, easiest, and surest method of emptying the lower bowel. To an infant this may be given with a 4-ounce infant's syringe, but one bulbful may not be enough. Sometimes it is necessary to give several to make the bowels move adequately. One bulbful which produces no result is a mere gesture, not an enema! Older children need more liquid, up to a pint or more, and the fountain syringe is the easiest way to give it. After the initial emptying of the bowel, one should take thought for the morrow. Enemas are a nuisance to mother and child, and one may well avoid them when possible. A mild laxative should be given each night to a sick child unless there is diarrhea. He will be inactive and on a low diet, and the chances of a normal morning movement without help are slim indeed.

The laxative of choice is the one which the mother has found useful in the past, the one which the child will take, and the one which works. If the child has never had a laxative, the physician's choice is free. Like all medicines given children, the laxative should be as palatable as possible. Milk of magnesia straight, in orange juice, or in milk, is most frequently used. Infants and young children take it well, and it is usually effectual. An infant needs $\frac{1}{2}$ to one teaspoonful, an older child 2 to 4 teaspoonfuls or more. The mother usually knows the dose required. Older children may object strongly to the somewhat bitter taste, so another laxative must be sought. The aromatic fluid extract of cascara is a good laxative, but the bitter taste is poorly disguised and many children refuse it after the first dose. The plain fluid extract is much worse and should never be ordered. Various syrups containing senna are palatable and effectual. Syrup of senna, U.S.P., may be used, but in the family medicine

cabinet Castoria or Syrup of Figs is usually found. If the child will take either one, and if it has been effectual in the past, we may close our eyes to the fact that these are proprietaries. Phenolphthalein in flavored tablets or in chewing gum is a good laxative when it works, but is not effectual with all children. Salines are more or less unpleasant to taste. The carbonated solution of magnesium citrate is the only pleasant one, but many children object to carbonated drinks, and the dose is bulky. Bicarbonate of soda is the simplest and one of the best salines but one which is rarely used; indeed, many do not realize that it acts as a laxative. Like all salines it should be given first thing in the morning, half an hour before food, and in a very cold solution. One-half to one teaspoonful dissolved in 4 ounces of water, which is then iced, makes a solution not too unpalatable, which older children may take. Of the other salines, Rochelle salt (sodium and potassium tartrate) is least unpleasant. In some instances a laxative like phenolphthalein may be given at night followed by a small dose of sodium bicarbonate next morning. This combination is useful in children who fight enemas too much and with whom laxatives do not work well. Sugar-coated pills may be given older children but obviously have no place in the treatment of young ones, who may chew them and get the bitter taste. Mineral oil, plain or in emulsion, is useful in chronic constipation but is not reliable in acute illness where something stronger is needed.

Certain symptoms make the patient so uncomfortable that they demand treatment.

Fever is probably not altogether undesirable, for it is nature's method of fighting infection. Nevertheless it makes the patient restless and uncomfortable, causes muscular aches and pains, and may disturb sleep. High fever in itself may become dangerous, especially to the child who has the tendency to convulsions. It is justifiable to try to keep the fever from becoming too high, even though we know we are not curing the patient by merely reducing it temporarily.

Aspirin is the drug most often used and it works well, except in the rare cases of idiosyncrasy. The dose need not be large. The rule of giving drugs by weight works for almost all drugs, and aspirin is no exception. For example, an adult will take 10 gr. to relieve the symptoms of fever. If we consider the average adult's weight as 150 pounds, then the dose per pound for a child is $\frac{10}{150}$ or $\frac{1}{15}$ gr. The doses commonly given will approximate this very closely. All tablets should be crushed and given with sugar and water from a spoon. They may be mixed with honey, jelly, applesauce, or even concealed in a small chocolate drop as a last resort. Aspirin may be repeated safely every three hours if the temperature is over 102° F.

Hydrotherapy is useful in reducing fever, but it is often ordered and administered unwisely. Cold sponges or alcohol sponges are resented bitterly by many children and are uneasy and troublesome to give. A tub bath is much easier, just as effectual, and the child is accustomed to it. The water need be little if any cooler than the usual bath, for with the higher temperature of the child a bath at 98° to 100° F. is enough below his body temperature to be an effectual means of reducing it. The warm bath brings blood to the surface, from

which it is often driven in fever by spasm of the peripheral vessels, and so lets the body radiate heat. The cold sponge bath merely chills the surface further, and its actual cooling capacity does not make up for this fact. The drop in body temperature after a warm bath is often greater than from a cold sponge. Infants and young children are easily carried to the bathroom, and older children can usually walk there, except in grave illness when it is, of course, necessary to use a bed bath. Care must be taken not to overheat the bathroom during the bath, which is bad for both patient and nurse. Aspirin may be enough when the temperature reaches 102° or 103° F., but when it is 105° F. or more both aspirin and hydrotherapy should be given in order to reduce the fever promptly. We must not forget the possibility of a convulsion from hyperpyrexia.

Pain is associated with fever (general aching) or with complications, such as otitis frequently, and pleurisy less often. Aspirin is adequate for the muscular pains of fever but is not enough for severe pain. Phenacetin (acetphenetidin) is the best of the coal tar analgesics, although it has apparently been forgotten by many medical schools. Pyramidon had supplaced it almost entirely until the dangerous effect on the bone marrow was discovered. Phenacetin has little effect on bone marrow, has little taste, and is effectual in relieving pain. Its dose is about the same as aspirin, roughly $\frac{1}{15}$ gr. per pound. It may be combined with aspirin or with other analgesics.

Codeine is the best of the morphine derivatives for pain in childhood, but the dosage ordinarily used is too small. It should be calculated on the basis of a real pain-relieving dose in an adult, which is a full 2 gr. This gives $\frac{2}{150}$ gr. or $\frac{1}{75}$ gr. per pound for the child. At 15 pounds the dose is then $\frac{1}{3}$ gr., at 25 pounds $\frac{1}{2}$ gr., and at 50 pounds $\frac{2}{3}$ gr. One sees a dose of $\frac{1}{4}$ gr. ordered for a large child with no relief from pain. For an acute earache the combination of codeine and phenacetin is most useful. If a child is subject to earache with every cold, the mother should have on hand powders containing phenacetin 1 to 3 gr., codeine sulfate $\frac{1}{4}$ to $\frac{1}{2}$ gr., sugar 10 gr.

Restlessness and inability to sleep are frequent and important symptoms of acute respiratory disease needing attention. They may be due to nasal obstruction, to cough, to pain in throat, ear, or pleura, or merely to the general discomfort of fever. In any case the child is entitled to his sleep, for lack of it lowers his resistance. Furthermore, the parents need their rest. A mother who is up many times a night is likely to acquire a cold herself from fatigue and chilling, as well as from contact with her child's infection, and a sick mother is no help in the problem. We must not forget the father, who has to support the family, for if he gets sick, economic strain or even disaster may result.

It may be that treatment of the obstructed nose and relief of the cough or pain may allow the child to sleep, but if he is still restless the mother should be prepared to meet the situation. She should have a sedative on hand with instructions to use it if needed, rather than to wait until midnight or later, when drugstores are closed and the doctor should be asleep. The pediatrician needs only a few drugs in the sedative group. Phenobarbital is the best and most often used. The doses prescribed are often too small, for children are quite tolerant of the drug. The dose may be calculated on the basis of weight. A full hypnotic

dose for an adult is 3 to 4 gr. A child will take $\frac{1}{50}$ to $\frac{1}{40}$ gr. per pound. Young infants tolerate $\frac{1}{4}$ gr., and in the second year $\frac{1}{2}$ gr. is not too much, but $\frac{1}{4}$ gr. is not enough for a husky 2-year-old. Even larger doses than these may be needed and are well tolerated. Some children are affected so little by phenobarbital that some other drug must be used. For many years I have relied on carbromal (Adalin; bromdiethylacetylurea). This remedy is apparently not stressed in most medical schools, for I have rarely met a physician who uses it and many druggists do not keep it in stock. It is safe, quite efficacious, and leaves the patient (from my personal experience) with less of a "head" than the barbiturates. The full dose for an adult is 10 gr., so a child may take $\frac{1}{15}$ gr. per pound. Most children to whom I have given it sleep well one or two nights and are relaxed and quiet next day. I have seen no bad effects. It is also useful for a nervous, jittery child after an accident, operation, or any unusual upsetting experience.

When a child is vomiting incessantly, or after a convulsion, or where heroic sedation is indicated, sodium amytal in suppository or even intravenously is useful. The dose by rectum may be about that of phenobarbital.

Nasal obstruction from swollen turbinates and discharge demands attention. We cannot stop the inflammatory process, but we can relieve the discomfort and diminish the dangers of some of the complications. Obstruction increases the likelihood of the development of sinusitis and otitis media. The list of agents which shrink the nasal mucosa is long. Many manufacturers produce them, a new one every year. Adrenalin and ephedrine have been followed by other substances which are said to give less local irritation and secondary reaction. The fashionable ones today are neosynephrin and Privine, although others may be as good. Solutions and jellies each have their advocates, and patients have their favorites. Jellies have certain advantages over drops. They stay in the nose longer and hence give a more prolonged action. Drops run through the nose so fast that their action is brief, unless care is taken in their administration. In using nasal jelly the tip of the tube containing the jelly should not be inserted into the nose, for it may hurt the child and the mother cannot see the amount administered. The tip should be kept outside the nostril and a drop of jelly just large enough to fill the nostril should be squeezed out. The child's mouth should then be closed by pushing up the jaw or holding the lips, preferably at the end of an expiration or cry. The resulting deep inspiration will then draw the jelly well into the nose. Older children will snuff it up voluntarily. Given in this way, few children will object to the jelly, although the mother often claims that it has been fought bitterly in the past. It is amusing to see her chagrin when the proper method is demonstrated and the child makes no objection. If drops are used, the child's head should be held in the inverted position, hanging down over the mother's lap or the edge of the bed. This position should be maintained for three to five minutes so that gravity can carry the solution to the upper and the middle meatus. When the head is upright or the chin merely elevated, the solution runs down the floor of the inferior meatus into the nasopharynx and may never touch the turbinates. Silver preparations (argyrol, neosilvol) may be used for children whose nasal dis-

charge is purulent or turbid. The indiscriminate use of these preparations in all cases of coryza is not necessary. The danger of argyria from long-continued use must not be forgotten, and mothers should always be warned not to use silver salts more than a few days at a time.

Cough in itself is not altogether a serious symptom, for by it the child clears accumulated mucus from the air passages, and it is not desirable to suppress it entirely. However, cough can be so frequent and severe that the child rasps his mucous membranes unduly, and so provokes further irritation. It is well to keep coughing under control. Cough can originate in any part of the respiratory tract, from the tickle of nasal mucus to that of a deep-seated bronchitis. We can judge the cause of cough by its character and by the physical signs, or lack of them, as in acute tracheitis. The cough from nasal mucus or from a dry pharynx merely needs treatment of the nose and throat. When it arises lower down it is usually necessary to give some cough medicine, partly as a placebo to the parent. Cough remedies are numerous, many of them worthless, most of them mildly effectual, none of them perfect. Some of the older ones, like Stokes' Mixture or those containing ammonium chloride, are unpalatable or nauseating. Of all the "expectorants," ipecac seems to be the only one which is worth using. In emetic doses it certainly increases the flow of mucus, but whether small doses alter the quality of the mucus or influence the inflammation of the bronchial mucosa is a matter of dispute. It does no harm at least, in small doses, and seems to do some good. Infants will tolerate 1 to 2 drops every three hours and older children up to 5 drops, but some children vomit with these doses and the amount must be reduced. Most cough mixtures contain codeine, and this drug certainly diminishes the irritation of a too-frequent cough. The great majority of medical graduates know only one cough medicine, codeine with elixir of terpin hydrate. I believe that the latter is worthless and that we ought to be able to write a better prescription. For a good many years I have used and taught the use of the following mixture. Many of my students agree that it is as good as any:

			Approximately	
R	Codeinae Sulfatis	gr. ʒ	0	3
	Syr. Ipecac.	5 ii	7	5
	Tr. Persionis	5 i	3	0
	Syr. Tolutani	q.s. ad ʒ vi	180	0
M. et Sig: One teaspoonful every 3 hours (after food).				

This gives a dose of about $\frac{1}{4}$ gr. of codeine per teaspoonful. (Note: There are only six average teaspoonfuls in one ounce, *not eight*, or 5 c.c. to a teaspoon. *not 4 c.c.*) The amounts may be varied for age, or fractions of teaspoonfuls may be given to a younger child. The tincture of eudbear (persionis) is merely a coloring substance, deliberately put into all codeine mixtures. Its color makes certain that the mother will know what she is giving, and she can tell the physician that she needs more "red medicine." The point may seem trivial to the pure scientist, but to the practitioner it is one of importance. Syrup of tolu is said to have some expectorant properties. Other flavors may be more pleasing, such as syrup of orange, lemon, or wild cherry. In many instances an adjuvant to

the codeine, such as an antispasmodic, may be wanted. Antipyrine is useful for this purpose, and moreover is analgesic and antipyretic. It has the advantage of being the only water-soluble coal tar analgesic. One grain, more or less, per dose may be added to the previous mixture, usually 15 to 30 gr. to the 6 ounces.

Another ancient and time-honored cough medicine is the *mistura glycyrrhizae composita*, or Brown Mixture. While this is an old shotgun, it has some uses still. In the first place, it can be bought over the counter by the mother, on telephone advice, without the delay of getting a prescription and having it filled. Second, it is palatable and harmless. It contains little opium (approximately $\frac{1}{25}$ gr. per teaspoonful). The potassium and antimony tartrate is said to be an expectorant. The other ingredients are inert. I often suggest adding a drop or two of syrup of ipecac to a dose. But I suspect the greatest value of Brown Mixture is as a placebo, so that the mother who demands a cough mixture will be satisfied and the infant not harmed. It is safe enough to give small infants 10 to 30 drops and older children 1 to 2 teaspoonfuls. The amounts printed on the labels of bottles sold over the counter are too small.

One other drug useful in persistent or chronic cough is potassium iodide. This was an ingredient of all the old shotgun mixtures, but is rarely used for children. It certainly changes the character of expectoration, making it thinner and less sticky, and it is occasionally useful. It is usually prescribed in essence of pepsin or in an elixir, to be taken in milk. Ammonium chloride should not be given on account of its bad taste and doubtful value. The rest of the expectorants act more or less like ipecac and are not as good.

Among other means of stopping an irritating cough is warmth over the trachea, from a warm-water bag or a piece of flannel or woolen cloth around the neck. Hot or cold wet applications and counterirritants are not necessary. Cough lozenges are often useful to allay a cough from a tickling throat. Their value comes mainly from the sugar, although the menthol in some of them may help. Local applications to the chest may have some value. Camphorated oil and mustard are traditional remedies. If mustard is used it must be watched carefully or the skin may be burned. A thickish paste of mustard, 1 part, plus flour, 6 to 8 parts, wet with cool water, not hot, spread on cotton cloth, may be left on for three to five minutes but not much longer. Most mothers apply counterirritants to the sternal region. If used at all, they should be applied to the lateral and posterior parts of the chest. Their action, if any, must be purely a reflex one by stimulating the skin nerves, and there is no excuse for using counterirritation, except possibly in a deep-seated bronchitis.

Croup is a symptom which demands prompt attention. There is nothing so terrifying to a mother as to have her child waken choking and struggling for breath (almost always between 11 P.M. and 1 A.M.). Nothing gives such prompt relief as an emetic, and syrup of ipecac is the best and the most palatable. It is wise to have a fresh bottle of it in the patient's house in the winter months, especially if the child is prone to attacks, for drugstores are usually closed during the croup hours. (It is also a great help to have it handy when a child swallows poisonous substances.) The doses of ipecac on printed labels are often too small:

"five drops every fifteen minutes till vomiting occurs." We want prompt emesis, and there is no overdose of ipecac. It should be given in teaspoonful doses, repeated just as fast as the child can take it. My favorite method of impressing this matter is to tell the mother to give it until the teaspoonful going down meets the one coming up. Vomiting usually relieves the spasm of the glottis, and the child breathes more easily. Ipecac should be given in smaller doses for a few days, usually with codeine as previously described, to prevent the recurrence of croup a second or third night. It is well to waken the child at 9:30 or 10 P.M. the second and third night to give cough medicine and water, which prevent the drying of the laryngeal mucus into crusts, the real cause of the spasm. External dry warmth over the trachea is especially helpful in croup. Wet compresses are no better and are more trouble. The traditional croup kettle for steam inhalation is much overrated. Croup tents give too much steam and are too hot. Many children have been burned by the steam, and beds have been set on fire with alcohol lamps. The latter also may give off formalin vapor, which is decidedly undesirable. An open pan of boiling water in the room does no harm and placates the parent at least. Steam inhalations are impracticable for children and of doubtful value, since the steam hardly reaches the vocal cords at best.

Bronchospasm accompanies many cases of bronchitis, as well as true bronchial asthma. The latter is an allergic phenomenon primarily and cannot be discussed here, but there are many children who occasionally have more or less severe attacks of spasm of the small bronchi with ordinary bronchitis. There may be an allergic factor in these children, but they do not belong in the same group as chronic or seasonal asthmatics. The amount of discomfort caused by bronchospasm varies greatly. Some children are most uncomfortable from the dyspnea produced, but others, especially infants, seem to mind it very little. The spasm can be relieved by adrenalin solution 1:1,000 intramuscularly, but it is wise to give small doses at first until the susceptibility of the patient to the drug is ascertained. One to three minims (0.065 to 0.2 c.c.) is enough to relieve many patients, while 10 minims (0.6 c.c.) may give distressing cardiac symptoms. Adrenalin in oil may be used for a more prolonged effect.

Theophylline or aminophylline will relieve many patients as effectually as adrenalin. They may be given by mouth or by rectum and are often combined with phenobarbital to counteract the caffeinelike effect which makes the patient wakeful and restless. They often cause vomiting even when given by rectum. (Sodium amytal may be given by rectum to control the vomiting.) The patient who is subject to attacks of bronchospasm does not have to wait for the doctor's visit, if a supply of tablets or suppositories of these drugs is kept in the house. They have the advantage of sparing the child the pain of an intramuscular injection. Benadryl and Pyribenzamine relieve the nasal obstruction of allergic rhinitis, but I have seen little or no effect on bronchospasm.

Otitis media is such a frequent complication of colds that it deserves brief consideration. The first indication is to relieve pain with phenacetin or codeine or both. External warmth may help. Thorough shrinking of the nasal mucosa

should be prompt, for only by decreasing congestion in the nose and nasopharynx can the ear be drained through the eustachian tube. Antibiotics in full doses should be given at once. Sulfonamides are usually effectual, penicillin rarely necessary. The general nursing care as previously outlined is essential. Local instillations containing glycerin and phenol are not necessary and without rational excuse. They are supposed to reduce the congestion in the middle ear and to relieve pain. The latter purpose is better and more promptly accomplished with analgesics. The pain of acute otitis lasts only a few hours, diminishing as soon as the nerves in the drum are no longer being stretched by increasing exudate. I have seen no more prompt relief from the glycerin and phenol preparations. If there is any wax in the ear, they make a mixture which is removed with difficulty. I have seen the drum turned gray by phenol by the formation of a superficial slough, but when this was wiped off, the drum was fiery red. Myringotomy is not needed as often as before the antibiotics came into use, but it cannot be entirely discarded. If the otitis does not resolve promptly, if the drum remains bulging and the temperature high, or if the drum perforates and the discharge remains profuse after three or more days, a myringotomy may be necessary to give drainage.

The abortive treatment of common colds by codeine, or codeine and paraverine, as proposed by Diehl, is often successful in adults. It must be used early, as soon as the feeling of irritation in the throat, slight nasal congestion, and general malaise make the patient realize that a cold is coming on. Unfortunately, the child does not often help the physician with this subjective information, certainly not until he is well along in childhood. Some intelligent and alert mothers are able to interpret the behavior of the child—slight droopiness, anorexia, change in the voice from nasal congestion—and can predict a cold's imminence. The parents of a few of my patients have been successful in aborting colds with codeine and papaverine. When the nose is running freely, it is too late.

The sulfonamides have changed the whole picture of acute respiratory disease in the last few years. They are useful only against secondary bacteria invaders and do not affect in the least the virus which usually initiates the infection. The full consideration of this group of drugs has no place in this discussion. Their greatest value is, of course, in pneumonia due to the pneumococcus or even to the staphylococcus, but the course of atypical pneumonia or virus pneumonia is unaltered. I have seen several patients poisoned by pushing sulfonamides unduly, just because there were persistent signs of consolidation in the lung. Failure to respond to sulfonamides is almost a diagnostic criterion for virus pneumonia. Otitis media, suppurative sinusitis, and cervical adenitis usually respond to sulfonamides. The difference in the course and duration of otitis especially is so remarkable that one must have lived through the two periods, before and after sulfonamide therapy, to appreciate it. Mastoiditis is almost an extinct disease.

The sulfonamides are two-edged swords, however, and the patient can easily be poisoned unless proper precautions are taken. With careful written instructions as to the exact dose and hour of each dose, and as to the necessity of giving

enough water and an alkali, the danger is minimal. The time has passed when every patient given sulfonamides must have a daily urinalysis and blood count. No community has adequate hospital or laboratory facilities to handle patients on that basis. We now know that toxic symptoms do not occur, or are extremely rare, if we use care in dosage and give enough fluid and bicarbonate. Orange juice is the easiest source of bicarbonate, and if a child receives the juice of three or more oranges a day we need not fear a too-acid urine. Bicarbonate as such is unpalatable, hard to administer, and produces gas in the stomach if acid gastric juice is present. Orange juice is palatable, well taken by most children, yields some calories in its sugar, contains ascorbic acid, which does no harm and may be valuable in infection, and helps increase the fluid intake when diluted with water. Citrate or acetate mixtures may be used if there is an orange idiosyncrasy, and even bicarbonate dissolved in iced water may be used for older children. Of the several available sulfonamides, sulfadiazine and sulfamerazine have fewer disadvantages than the rest of the group. They are rarely vomited, maintain an adequate blood level, and are not expensive. The dosage in most infections need not be high, not over one grain per pound in the first day and less than that thereafter. I rarely use sulfonamides for more than three or four days except in severe infections. If they have not done their work in that time they are unlikely to do so. I have made a practice of changing from one to another sulfonamide in patients for whom it is necessary to continue treatment more than four days or when a second infection or relapse indicates a new course of sulfonamides.

Tonsillitis with follicular membrane is one acute pyrogenic infection which does not always yield to sulfonamides in the doses usually given. Many patients will go on to the full four-day course with no apparent effect from the drug. This may be due to greater resistance of the staphylococcus, which is the organism usually present.

The status of sulfonamides as preventives is still questionable. In every acute respiratory infection the physician must ask himself, first, whether the symptoms are due to a virus infection or to bacterial invasion, and second, whether it is justifiable to administer sulfonamides in a case of probable virus infection to prevent secondary bacterial mischief. In an epidemic of colds, many or most of which are followed by otitis media, it certainly seems proper to give sulfonamides for a few days. But in a simple sporadic coryza it is still doubtful whether it is one's duty to give the drug. This question needs further statistical study on a large scale before we shall know the final answer.

Penicillin is in the limelight today and has proved its value in many serious infections, some of which do not yield to sulfonamides. Its uses and indications have been so thoroughly described that space need not be taken here. It is worth noting that penicillin has disadvantages. In the first place, it is still expensive compared with sulfonamides. Oral administration is not entirely reliable. Its parenteral administration is much more trouble, the frequent injections are time-consuming for the doctor or a trained nurse, and they are also painful to the patient. In the home, the single large dose in oil and wax is the best means of administration which we have at present. The aqueous solution, which must

be given every few hours means that the patient must be in a hospital, or have twenty-four hour trained nursing care. Much could be said about the disadvantages of hospitals for the child, of the psychic shock of removal from home, of the neglect which he regularly gets due to shortage and inexperience of nurses, of the difficulty of getting the orders of the doctor carried out, of the shortage of beds, and of many other undesirable aspects. Except for a few serious illnesses in which some special technique is required, most sick children are better off in a good home than in the best hospital. I must protest against the prevalent practice of sending children to hospitals and ordering penicillin for simple, self-limited diseases like tonsillitis, pharyngitis with fever, otitis, or even pneumonia. The cost of even a brief hospital stay, with laboratory work and penicillin, is an unfair burden to many families. Most of these acute diseases can be cured rapidly and efficiently at home with a carefully ordered nursing regime, and about twenty cents worth of sulfadiazine.

Summary

The successful treatment of respiratory diseases depends more on the general care and nursing of the patient than on specific remedies. A careful schedule must be planned with written instructions as to the exact hours for taking temperatures, feeding, giving medicines, and treatments. Symptoms such as nasal obstruction, cough, croup, pain, and restlessness may need treatment. Antibiotics are useful in the treatment of bacterial complications and perhaps in their prevention.

The following is an example of a useful printed form for routine use in treating acute illness:

CARE OF SICK CHILD

REST in Bed, Couch, Big Chair, Carriage. Child may sit up against pillows, need not lie flat.

Bed table or lap board with small toys will keep child amused.

Keep warm with light robe or sweater over night clothes while sitting up.

Bedding must not be too heavy, one or two light blankets only.

AIR Keep fresh by opening window often, avoiding direct drafts. Room should be 68°-70°, not warmer.

BATHE each day, sponge or tub.

EVERY 3 HOURS

1. **TAKE TEMPERATURE** (rectal) and write it down.

2. **FEED** one or more of the following.....

3. **MEDICINES**, always after food Crush all tablets with sugar and water.

If 102° F. - Aspirin 1/2 tab. If 104° - bath, 5-7 min.

Telly in nose

Sulfa tablets - (1) Mon at 10 - 4 - 10

Tues " 7 - 12 - 7

Wed " 7 - 12 - 7

Cough Med. 1 tsp.

If in pain and restless - give 1/2 "pain tablet" and 3 small tablets

BOWELS must be kept open each morning.
Laxative each night while ill.

Enema each morning, if no movement by 10 AM o'clock.
Use soapy water and give enough to obtain a good movement.

Milk of Mag. 2 tsp

Hours
7 Cereal, with little milk
Toast

10 Orangeade

1 Soup, crackers
Ice Cream or Junket

4 Orangeade

7 Cereal or Milk Toast
Cooked Fruit or Jello

10 Orangeade

WATER between feedings
As Child improves add

Milk
egg, Mat, Veg.

FIG. 1.

THE PREVENTION OF RESPIRATORY INFECTIONS

In order to prevent respiratory diseases we must have a clear conception of their etiology. The causes of these infections are numerous and complex. They may be divided into groups for clearer understanding.

General Causes.—Crowding in cities, in buildings, in schools, in vehicles, trains, and so forth, obviously increases contact and the opportunities for transfer of infecting agents. Civilization may thus be blamed as the underlying cause of most respiratory disease. The fact needs no repetition that explorers and men in lumber camps and other isolated situations do not have colds until they return to civilized places. Smoke, dust, and pungent fumes add to respiratory tract irritation. Climate in general affects the number of colds in a population, but changeable weather is worse than steady cold, and warm climates are not entirely free from respiratory disease.

Individual predisposition depends to some extent upon abnormalities of the respiratory tract, such as nasal obstruction from septal deviation, adenoids, or greatly enlarged tonsils. Allergy plays a part in the matter, for it not only causes hay fever and asthma, but predisposes some children to respiratory infections as well. This relation is complex, and we have not yet fully solved it. Individual predisposition to a particular kind of cold is frequently seen. Some children always have laryngitis or croup, others have sinusitis or otitis, others bronchitis or asthma, and each is likely to stick to his favorite type of disease.

Precipitating Causes.—These are not always given the consideration they deserve. In every acute infection there must be a set of circumstances which makes the child become ill.

Direct contact with an acute infection or possibly with a carrier of an infecting agent is responsible for many colds. A parent, a servant, or even a casual visitor often brings in a cold, which then spreads around the family unless superhuman vigilance is taken to isolate the first victim. Not all colds, however, can be traced to this source. Many children become ill without discoverable contact. Factors which lower the resistance of the individual are as important as the infectious contact, for with lowered resistance the organisms which are ever present in the nose and throat easily become active. These factors must be appreciated, for it is by attention to them that we may hope to make colds less frequent. They may seem to be only remotely or occasionally responsible for acute or recurrent colds, but careful histories will bring out a very close connection between colds and certain antecedent circumstances.

Digestive disturbances certainly predispose to colds. Indigestion may come from overeating, or from eating indigestible or improper food, or from habitual irregularity of diet, or from eating trash of all sorts. The slight but persistent disturbance due to taking milk or other hearty foods between meals is one of the most common causes of recurrent colds in many children. Stopping the milk, which has been forced upon children in school at mid-morning recess, often diminishes the frequency of colds. This is not a theoretical matter but a fact, based upon careful observation of many children in whom the association is too frequent to be accidental.

Constipation is frequently to blame. The child who skips his daily movement, or who postpones it until late in the day, absorbs toxic substances which surely lower his resistance. If he goes off to school with an empty stomach and a loaded bowel day after day, it is small wonder that he is an easy prey to infections.

Fatigue lowers resistance, and this may be acute fatigue from unaccustomed overexertion or from continuous overactivity, or chronic fatigue from insufficient rest at night or too early omission of naps in the runabout age period.

Chilling is perhaps the most frequent direct cause of colds. We call respiratory infections "colds" because they regularly follow chilling. Cold weather is most dangerous when accompanied by high winds. Adults may not appreciate how much a small child is chilled by cold winds, especially with insufficient out-of-door clothing, even when the temperature is not extremely low. Much could be said about the vagaries of fashion in dressing children, as well as their parents. Bare legs and arms in windy winter weather cannot fail to subtract heat unduly from the child's body. The uneven heating he gets by being bundled up in many layers, except over his legs, is perhaps the worst factor. A girl of 3 years was once brought to my office on a bitter winter day with nine layers of woolen cloth and a fur coat down to her hips and below this a pair of silk socks and thin pumps! Her legs felt like marble, but it had not occurred to her mother that this was an unreasonable costume. Indoor clothing in winter is often insufficient. Even in a house adequately warmed there is always a cold air current on the floor, and it is on the floor that children spend most of their time. Bare legs and arms on the floor easily become chilled. Light overalls and long sleeves give a better protection than the light cotton dresses commonly worn indoors, which are no warmer than those worn in the summer heat. Chilling at night is common in infants and young children. The infant who is put to bed with loosely applied blankets soon kicks them off and becomes chilled. The nursing profession has never solved this matter, and babies in hospitals are terribly neglected in this respect. A baby in the split-back nightgown and a wet diaper, with no blankets over him, is a common sight in pediatric wards. The uncovered infant and runabout is inviting respiratory infection, for the body needs more even covering and temperature in sleep than in waking hours. Clothing manufacturers have met the problem by offering the "sleeper"—a heavy flannel pajama with feet, advertised "to keep the baby warm when he crawls out." Mothers usually leave on the shirt (often double breasted) under the sleeper. The result is that the child is soon too hot and does crawl out, if he is able, but even the sleeper and shirt do not keep him as warm as would a blanket or two. One keeps warm in bed with bedding, not with heavy night clothes. We have met this problem satisfactorily by using a simple bag made of a folded light blanket for infants, and for older children a nightgown with a tape or band at the tail which is tied to the foot of the crib or to the bedspring. With blankets properly fastened to the crib rods, the child stays covered all night. His mother does not have to get up repeatedly to see that he is covered. If her rest is disturbed, she may take a cold which she then transmits to the child! Uncovering is a serious matter, and until the problem is met in every case we must expect defeat in our effort to prevent a child from having recurrent or persistent colds.

Overheated houses are responsible for many respiratory infections. The hot air dries out the mucous membranes, and the heat makes the child perspire.

Any moving current of air may then chill him. In the houses of the well-to-do, where thermostats regulate heat accurately, this is less a factor than in homes heated with stoves, pipeless furnaces, or unregulated steam. Apartment dwellers, who are afraid they will not get their money's worth of heat and who leave their radiators turned on all day, are among the worst offenders. Mothers who wear a thin cotton dress and little else, with bare arms and legs, too often keep the house at a temperature suitable for their costumes, but not healthy for their children. Overheating and subsequent chilling in summer may also precipitate illness. Long exposure on sea-beaches, staying too long in the water, hose parties in the back yard, may be followed by acute colds or tonsillitis. The latter occurs more often in summer than coryza or bronchitis; indeed, tonsillitis is the most common acute illness seen in summer.

Any one of the factors just discussed may cause a child to acquire a cold, but it may take more than one of them. It is a common experience to elicit the following history from a mother whose child has an acute febrile respiratory disease: The child on a holiday skipped his usual morning movement, went on an expedition on which he became overtired, had no midday rest, perhaps was chilled in the water, ate unusual foods at irregular intervals, returned late in the evening, and slept restlessly. Next day he pays the penalty for the debauch by being acutely ill. Whether he has nasopharyngitis, tonsillitis, laryngitis, or bronchitis depends mostly on his own inherent tendency to a particular localization. Direct contact with another infection is not necessary in such cases, yet this child may transmit his activated infectious agent to his siblings.

Vitamins, cod liver oil, and tonics may help build up a child's physical resistance but will not prevent colds if he leads an unhygienic life. Bacterial vaccines by mouth or by injection cannot prevent the virus infections, and it is doubtful whether they build up immunities to secondary invaders. Some patients insist on having cold injections and claim that they have fewer or less severe colds when they receive them. The effect is probably psychic, or they may take better care of their own health in order to be sure the injections do some good. There is no reliable evidence that such injections are justifiable.

In attacking the problem of recurrent or persistent colds, the first step is a careful study of the child's environment, of his diet, and his daily regime. We may be unable to change his home, but we can inspect it and determine whether it is under- or overheated. The child's bedroom, the situation of his bed in relation to windows and doors, the bedding, and night clothes must be studied, and the mother must be taught how to keep him covered and out of direct drafts. His indoor and outdoor clothing must be adequate. The daily regime must be studied from the hour of rising to bedtime and must be carefully arranged. A morning movement must be insisted upon, and this means an early breakfast, one hour before leaving for school, so that there is time for a bowel movement. The diet must be prescribed in writing, and special stress should be laid on the disadvantage of milk between meals. Rest for preschool children after lunch, and for school children on week ends and holidays, helps avert fatigue. The Sunday fatigue from overexertion often precipitates the Monday cold. Careful

physical examination must be made for defects, especially malnutrition, anemia, and nasal obstruction. If remediable, these must be corrected.

With a complete study of all factors we can make colds less frequent, and with earlier treatment usually make them less severe. The child's surroundings can be controlled to a certain extent, depending upon the locality in which he lives, his home and economic status, but most of all on the intelligence and co-operation of his parents. When parents are not bright enough, or too lazy, to follow advice or instructions, the child is bound to be ill from time to time. Some factors cannot be eliminated, especially contact with cases of virulent infections. So children will continue to have a cold or two each winter under the best of care, just as do their parents and their physicians!

Clinical Conference

CONFERENCES OF THE CHILDREN'S HOSPITAL WASHINGTON, D. C.

1. Conference on Infantile Cortical Hyperostoses (Caffey-Smyth Syndrome)

DR. FREDERIC G. BURKE.—R. G., a 3½-month-old white male infant, was first admitted to Children's Hospital on May 25, 1946, with the chief complaint of fever and irritability. The illness had begun one week previously with a swelling about the right side of the face. This was associated with irritability, which, together with the fever, continued on up to the hospital entry. The day before admission the temperature rose to 105° F., at which time the child seemed to have some twitchings of the arms and legs, but there were no frank convulsions. The past history revealed the child had had some difficulty with his formula at the age of 4 weeks and also had had some mucus and blood streaks in his stools. The formula was adjusted several times, and the stools became normal. The baby gained weight in a normal fashion. Vitamin supplements had been administered in adequate amounts since the age of 4 weeks.

The family history revealed that the patient's paternal aunt had had active tuberculosis six years previously and that she had been in a sanatorium where a pneumothorax and phrenicectomy were done. Allegedly, her infection had been inactive for the past four years. She took care of the baby for four to five days during the second week post-partum and wore a mask during this time. She had also visited the baby intermittently since then. The child's mother had always had negative chest x-rays and sputum until two or three weeks previously when a chest x-ray was thought to show some calcification in the right lung. The mother had had several episodes of pleurisy since the age of 16. A sputum examination done on the mother shortly before the infant's admission was negative for tubercle bacilli.

Physical examination at the time of admission revealed a well-developed, well-nourished 3½-month-old infant who appeared acutely but not critically ill. The temperature was 104.4° F. There was a swelling on the right side of the face which extended superiorly to the upper level of the ear and down to the angle of the jaw. This area was tender and indurated but nonfluctuant. There was no inflammation of Stensen's duct and no palpable calculi. The liver and spleen were palpable one fingerbreadth below the costal margin. The heart and lungs were negative, and the remainder of the physical examination was essentially normal.

Cases presented from the Medical and Surgical Services, Dr. Joseph E. Wall, Chief of Staff

Laboratory examination showed a hemoglobin of 8.5 Gm. with 3.2 million red cells; the white cell count was 14,100 with 66 per cent polymorphonuclear cells, 29 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophiles. Platelet count was 150,000. Subsequent repeat hemograms showed a consistent leucocytosis ranging between 13,000 and 16,000 with an essentially normal differential. Urinalysis was negative. Examination of the spinal fluid was negative as were the febrile agglutinins. An x-ray of the chest revealed a pericardial shadow in the third to fifth interspace on the left, the nature of which was not known. Roentgen examination of the bones of the face revealed no evidence of periostitis at this time. Complement fixation test for mumps performed at the National Institute of Health was reported as negative. A tuberculin test (O.T. 1:1,000) was done, and within twenty-four hours an area of erythema measuring 2 cm. in diameter was observed. However, this erythema subsided so that at the end of forty-eight hours it was only minimally present. A repeat tuberculin test (O.T. 1:100) was negative, and P.P.D. No. 2 similarly showed no positive reaction. Gastric washings for tuberculosis organisms were performed at this time, and of five consecutive examinations, four were positive for tubercle bacilli on smear, while culture of the washings on Petraghani's media grew out tubercle bacilli on three occasions. A provisional diagnosis of primary tuberculosis was made on the strength of these positive gastric washings.

During the course in the hospital the child's temperature fell gradually during the first week and then remained low grade. The swelling upon the right side of the face subsided somewhat but did not completely disappear, and it remained quite tender. The baby took his formula moderately well and gained weight. Therapy during this admission consisted of penicillin (20,000 units every three hours for seven days) and then sulfadiazine for four days. However, neither drug appeared to exert any favorable influence on the course of the disease. He was discharged after a twelve-day hospital stay to be followed in the dispensary.

At home the child continued to have a low-grade fever and was moderately irritable. The swelling of the right side of the face remained and occasionally became more marked. About two weeks after discharge it was noted that the left side of the face was becoming similarly involved. One week later a painful tender swelling was noted along the left forearm. An x-ray of the long bones taken at this time showed a periostitis along the shaft of the left ulna at the distal end, and it was thought that this lesion represented a tuberculous periostitis. The child was then readmitted to the hospital for treatment with streptomycin.

Physical examination at this time revealed a fretful 4-month-old infant who appeared chronically ill. Both sides of the face showed a marked, brawny, tender edema extending from the lower lobe of the ear to the angle of the jaw (Fig. 1). Stensen's duct did not seem to be involved. There was a diffuse swelling and marked tenderness along the distal end of the left arm. Heart and lungs were negative. The liver and spleen were palpable one fingerbreadth below the costal margins. The rest of the examination was essentially negative. The temperature was 102.6° F.

Laboratory examination revealed a hemoglobin of 10 Gm. with 3.5 million red cells; the white count was 27,000 with 53 per cent polymorphonuclear cells, 46 per cent lymphocytes, and 1 per cent eosinophiles. Repeat urinalyses were negative. The blood culture taken shortly after entry was sterile. Sedimentation rate was normal. A gastric washing performed prior to the initiation of streptomycin therapy revealed a rare acid-fast bacillus on smear. X-ray examination of the long bones of the upper and lower extremities revealed some periosteal thickening of the bones of the upper extremities with some increase in the width of the distal portion of the ulna (Fig. 2). X-ray examination of the chest revealed no essential change since the previous film taken on May 29.



Fig. 1.—R. G. at the time of readmission to the hospital. Note the marked bilateral facial edema.

Roentgenologic examination of the skull in the anteroposterior and lateral positions revealed no definite evidence of abnormality. Wassermann and Kahn tests were negative. Serum calcium was 11.5 mg. per cent and phosphorus was 3.3 mg. per cent. The ascorbic acid level was 0.369 mg. per cent. A blood sample was sent to the National Institute of Health for complement fixation virus studies and was found to be negative.

On June 27, the day before the second admission, the patient was started on streptomycin with a dose of 30,000 units every three hours intramuscularly. For the first two weeks in the hospital the temperature remained elevated in the neighborhood of 101° to 102° F.; subsequently it came down to normal by lysis, and the child remained afebrile during the remainder of his hospital course. The patient slowly gained weight, and his appetite remained moderately good. The bilateral facial swelling gradually diminished and had completely disappeared within two and one-half weeks. Swelling and tenderness of the ulna also subsided progressively and disappeared in approximately the same interval of time. The sedimentation rate, which had been normal at the time of entry, rose to 39 mm. per hour (Winthrobe) within two weeks and remained substantially elevated (ranging between 22 and 45 mm. per hour) during the next month in the hospital. Repeated white counts showed a leucocytosis varying between 9,000 and 22,000 with the neutrophils ranging from 17 to 60 per cent.



Fig. 2.—R. G. X-ray of the extremities reveals a periosteal lamellated thickening of the long bones.

While on streptomycin therapy, repeat gastric washings were obtained for tubercle bacilli, and with the exception of one washing on July 11 which yielded a rare acid-fast bacillus on smear, all the other specimens, eleven in number, were negative both on smear and culture.

Within three weeks after admission, repeat x-ray examinations of the left ulna revealed evidence of healing of the periostitis noted at the time of admission. On August 12, x-ray examination of the thorax revealed some periostitis of the left clavicle and of the fifth rib anteriorly and the eighth rib posteriorly, similar in effect to the lesion involving the left ulna. A re-examination of the mandible on August 22 revealed a rather diffuse periostitis bilaterally on the inferior surface of the mandible. X-ray of the left ulna taken on August 28 just before discharge showed continued resorption of the previously described periosteal proliferation. On August 11 an exacerbation of the edema of the face was noted bilaterally and was quite tender and swollen. There was no concomitant temperature elevation, and the facial swelling subsided gradually during the course of the next three weeks with only slight residual nontender swelling remaining on the left side. Streptomycin was discontinued on August 17 after forty-seven days of therapy; the amount of drug administered totaled approximately 12 million units. No untoward effect from streptomycin was noted during the interval of its administration.

On August 22, one week prior to discharge, the sedimentation rate had returned to normal and the patient appeared clinically well. The infant was discharged on August 29, after a two-month stay in the hospital.

Follow-up x-ray examinations during the next six months showed continued and progressive healing of the previously noted areas of periostitis of the left ulna, clavicle, ribs, and mandible. The facial edema has completely disappeared, the temperature has remained within normal limits, and the infant appears completely well.

DISCUSSION

DR. SIDNEY ROSS.—This patient represented a diagnostic problem for a considerable period of time and probably would have remained so had it not been for the fortuitous simultaneous publication of a paper by Smyth, Potter, and Silverman,¹ in which were reported seven cases of a new syndrome which bore a striking similarity to our case. In common with our patient, the patients of Smyth and his associates showed marked irritability, fever, anemia, periosteal involvement, and a characteristic brawny, tender facial edema. There was little doubt following this report that our case fitted into this syndrome. Since attention has been called to the entity, nine additional cases of this syndrome have been diagnosed during the past eighteen months at Children's Hospital; two of the cases have been culled from our hospital records by reviewing all charts of infants under 6 months who had a discharge diagnosis of scurvy; a re-examination of their x-rays together with a review of the protocol indicated rather unequivocally that both cases were examples of this new disease entity. A detailed account of these cases will be discussed in a forthcoming report.⁴

In 1945 Caffey and Silverman² first described four cases of this syndrome, which they termed infantile cortical hyperostoses, presenting the symptoms previously noted. The basic roentgen change as described by Caffey was an external thickening of the corticalis, which was lamellated in many instances. Bones involved included the mandible, clavicle, scapula, ribs, and extremities. The soft-tissue swellings preceded the formation of the hyperostoses in the neigh-

TABLE I. A COMPILATION OF THE FINDINGS IN THE THIRTEEN INFANTS UNDER 7 MONTHS OF AGE REPORTED BY CAFFEY AND SMYTH

CASE NO. AND SEX	AGE OF ONSET	FEEDING HISTORY	FEVER	IRRITABILITY	BRAWNY EDEMA OF FACE	W.B.C.	TUBERCULIN TEST	VIT. C LEVEL (MG. %)	SEROL-OGY	SEDIMENT. RATE	OUTCOME
1 F	.5 mo.	Adequate	+	+	+	16,000-24,000	Neg.	0.12	Neg.	Elev.	Recov.
2 F	5 mo.	Adequate	+	+	+	12,000	Neg.	0.10	Neg.	Elev.	Recov.
3 M	7 mo.	Adequate	+	+	+	14,000-20,000	Neg.	0.085	Neg.	Elev.	Recov.
4 F	3 mo.	Adequate	+	+	+	23,000	Neg.	.44	Neg.	Elev.	Recov.
5 F	4½ mo.	Adequate	+	+	+	23,000-37,000		1.35			Recov.
6 M	2 mo.	Adequate	+	+	No	13,000	Neg.	Low blood, high urine	Neg.	Elev.	Recov.
7 M	2 mo.	Adequate	+	+	+	6,000			Neg.	Nor.	Recov.
8 M	2½ mo.	Adequate	+	+	+	14,000	Neg.		Neg.	Neg.	Recov.
9 M	3 wk.	Adequate	No	No	+				Neg.	Neg.	Recov.
10 F	4 mo.	Adequate	+	+	+	13,000	Neg.		Neg.	Elev.	Recov.
11 M	2 mo.	Adequate	No	No	+	11,000-21,000					Recov.
12 F	4 mo.	Adequate	+	+	+				Neg.		Recov.
13 M	3 mo.	Adequate	+	+	+	7,000-29,000	Neg.		Neg.		Recov.

TABLE II. A COMPILATION OF THE SITE OF PERIOSTEAL INVOLVEMENT IN THE THIRTEEN PATIENTS UNDER 7 MONTHS OF AGE REPORTED BY CAFFEY AND SMYTH

CASE NO.	MANDIBLE	CLAVICLE	SCAPULA	RIBS	EXTREMITIES
1	+	0	0	+	0
2	+	+	0	0	+
3	+	-	0	0	+
4	+	0	0	+	0
5	0	0	0	0	0
6	+	+	0	+	+
7	+	0	0	+	+
8	+	+	+	+	+
9	+	+	+	0	+
10	+	+	0	0	+
11	+	0	0	0	0
12	+	0	0	0	+
13	+	+	0	0	0
	12	7	2	5	8

boring bones and have occurred in the face, thorax, and extremities. The active manifestations in Caffey and Silverman's patients subsided completely after several weeks with no serious complications.

In spite of the general objections to eponyms in medical nomenclature, we have referred to the syndrome as Caffey-Smyth disease in our cases at Children's Hospital in view of the obscure etiology of the syndrome. In addition, it has been our impression roentgenologically that the skeletal lesion was primarily a periosteal reaction rather than a cortical involvement.

Thus far there has been a total of seventeen cases of this syndrome reported in the literature.¹⁻³ Of these, thirteen were in infants under 7 months of age. The ten cases of Caffey-Smyth syndrome diagnosed at Children's Hospital during the past eighteen months have similarly all been in children under 7 months of age.

A compilation of the findings in the thirteen infants under 7 months of age reported by Caffey and Smyth is set down in Table I. As will be noted, the feeding history including vitamin supplements was adequate in every case. Fever and irritability as well as the characteristic brawny, tender, nonhyperemic facial edema were noted in all patients but one. The white cell count was increased in the majority of instances, and there was usually a lymphocytic predominance. The tuberculin test as previously noted was negative in every patient where it was performed in the series reported by Caffey^{2, 3} and Smyth.¹ (In the case reported here the tuberculin was equivocally positive, but all our other nine patients had negative tuberculin tests.) Vitamin C levels were not singularly aberrant. Similarly the serology was negative in all patients. In the majority of instances where it was performed, the sedimentation rate was elevated. The periosteal skeletal involvement was widespread, as will be noted in Table II. The mandible was involved in every patient but one and accounted for the frequency of the brawny edema of the overlying soft tissue of the face; the latter was by far the most striking presenting symptom and permitted a provisional diagnosis to be made on sight in the majority of cases. The clavicle and extremities were other frequent sites of periosteal involvement. In one case seen at Children's Hospital, the only bony involvement was noted in the left scapula.

The etiology of this new syndrome remains obscure. Scurvy has been considered in the differential diagnosis in view of the periosteal bone involvement. However, the usually noted scorbutic bone changes, such as the zone of rarefaction beneath the epiphyseal line, the ground-glass appearance of the shaft, the Wimberger rings, and the absence of any subperiosteal hemorrhage on biopsy, would militate against a diagnosis of scurvy. In addition, the age of the onset of the syndrome (i.e., mostly 3 to 4 months) as well as the history of adequate vitamin C intake and lack of response to vitamin C would similarly be against a diagnosis of scurvy.

As for an infectious etiology, which is suggested by the increased white blood count, fever, and elevated sedimentation rate, there is not too much definitive evidence. Blood cultures and febrile agglutinations were negative in all cases, and there was no perceptible response to sulfonamides or penicillin. Biopsy specimens have similarly not been in keeping with a diagnosis of an infectious process. Smyth¹ and Caffey^{2, 3} mention that virus studies were not done in their cases. However, complete virus studies were performed at the National Institute of Health in five out of our ten cases, and all were negative. Syphilis can be ruled out on the basis of negative serologies, both in the patients seen at Children's Hospital as well as those reported by Caffey^{2, 3} and Smyth.¹ As for tuberculosis, we were initially under the impression that we were dealing with an acid-fast infection in the case reported here, in view of the positive gastric washings and history of exposure to tuberculosis. However, the generalized periosteal involvement was unlike the bony lesions described in tuberculosis, and, more important, the subsequent nine patients have had negative tuberculin tests and repeated negative gastric washings. Similarly in the seventeen cases described by Caffey and Smyth, tuberculosis was rather effectively ruled out. We can only conclude that the tuberculous infection in the present patient was co-existent and coincidental and was unrelated to the syndrome.

The possibility that the lesion may be of a sarcomatous nature as suggested by the laminated periosteal reaction is ruled out by the benign course of the disease together with the absence of any evidence of sarcoma on biopsy. Similarly, traumatic ossifying periostitis seems to be excluded. The disease at its onset may similarly be confused with parotitis as well as osteomyelitis of the mandible and neoplasm of the mandible.

In every case reported thus far as well as in our own ten cases, the disease was benign and ran a self-limited albeit a protracted course, sometimes lasting for months. The excessive irritability, slow weight gain, and poor feeding habits of the infant make this disease a sore trial for the parents. However, a good prognosis can be categorically given in every case once the diagnosis is made.

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2. Conference on Pericarditis With Effusion

DR. ELMER FANTAZIER.—M. M., a 5-year-old white girl, was admitted to this hospital on Jan. 19, 1948, with the chief complaint of fever and pallor.

The present illness began five days prior to admission when she complained of nausea and felt unusually warm. She vomited following breakfast and was unable to retain food for forty-eight hours. There was no diarrhea. The symptoms slowly subsided during the ensuing forty-eight hours, and the patient was allowed limited activity. On the morning before admission it was noted that the child was listless and had developed considerable pallor. On the day of admission she complained of pain in her left chest on movement, and the pallor was increased.

The past history revealed that the patient was the product of a nine months' gestation and an uneventful delivery. Her birth weight was 7 pounds. The neonatal period was not remarkable. Measles occurred at 4 years, from which she made a slow but uneventful recovery. The mother stated that the patient had had "flu" last winter, from which the convalescent period was about three weeks.

The family history revealed that there were two siblings, both living and well. There was no history of familial or constitutional diseases.

Physical examination showed a poorly nourished white girl who appeared acutely ill. The temperature was 100° F., and the pulse was rapid and thready. The blood pressure was 88 systolic, 58 diastolic. The skin was very pale and moist; no petechiae or rashes were noted. Palpable cervical nodes were present. The pharynx was moderately injected, and a thick white exudate was noted on the right posterior pharynx. There was a questionable friction rub over the lower left lung field anteriorly. The heart was enlarged to the left on percussion, and the sounds were muffled, distant, and rapid. No murmurs were heard. The liver was palpable three fingerbreadths below the costal margin. The spleen was not felt. A fecal mass was palpated in the left lower quadrant of the abdomen. No abnormalities of the extremities were noted, and the reflexes were physiologic.

An x-ray taken shortly after admission showed the heart to be enlarged to the right and left (Fig. 1). The cardiac contour was "water bottle" in type, indicative of dilatation and some pericardial effusion.

A blood count on admission showed a hemoglobin of 12 Gm. with 3.9 million red blood cells; the white count was 16,900 with 85 per cent polymorphonuclears. 8 per cent lymphocytes, and 7 per cent monocytes. Urinalysis was negative, as was the tuberculin patch test.

On the day of admission the patient was seen in consultation by Dr. Bernard J. Walsh.

The patient was given sulfadiazine initially in a dose of 7.7 gr. every four hours, and Digifolin, 1½ gr. three times a day, but she began to vomit the medications after the third dose of sulfadiazine. She was then given an infusion of 200 c.c. of 5 per cent glucose in saline slowly over a period of an hour, and penicillin was substituted for the sulfadiazine.

The child was fluoroscoped twice within twenty-four hours after admission. Following the second fluoroscopy, a pericardial tap was done by Dr. Walsh, and 200 c.c. of fluid were obtained; the first 20 c.c. were clear yellow, while the remainder of the fluid was a medium brown color. Following the pericardial tap there was considerable clinical improvement. Analysis of the pericardial fluid obtained from the tap was as follows:

	<i>Light Fluid</i>	<i>Dark Fluid</i>
Cells	5,000	8,000
R.B.C.	13%	8%
W.B.C. Polymorphonuclears	77%	91%
Lymphocytes	6%	1%
Mononuclears	4%	1%

Specific gravity: 1.018

Smear and culture of fluid: Negative.



Fig. 1.—M. M. X-ray of the heart taken on admission revealing considerable cardiac enlargement to the right and left. The cardiac contour has a "water bottle" appearance suggestive of pericardial effusion.

The patient has been on penicillin, 50,000 units every three hours intramuscularly, since the onset of vomiting on the second hospital day. She also received a maintenance dose of 8 minims of tincture of digitalis by mouth daily. The child is taking fluids well and eating soft foods now. The temperature has remained at about 100° to 101° F. since the pericardial tap on Jan. 20, 1948.

Clinically the patient has shown steady improvement. The heart continues to be enlarged to the left on percussion, but the heart sounds are more readily heard.

A chest film taken on the day of discharge is shown (Fig. 2). As seen by repeated fluoroscopic examinations, there has been considerable reduction in the cardiac-pericardial size. The pulsations along the cardiac borders gradually increased in amplitude. The liver enlargement slowly receded and became less tender. She was discharged on Feb. 2, 1948.

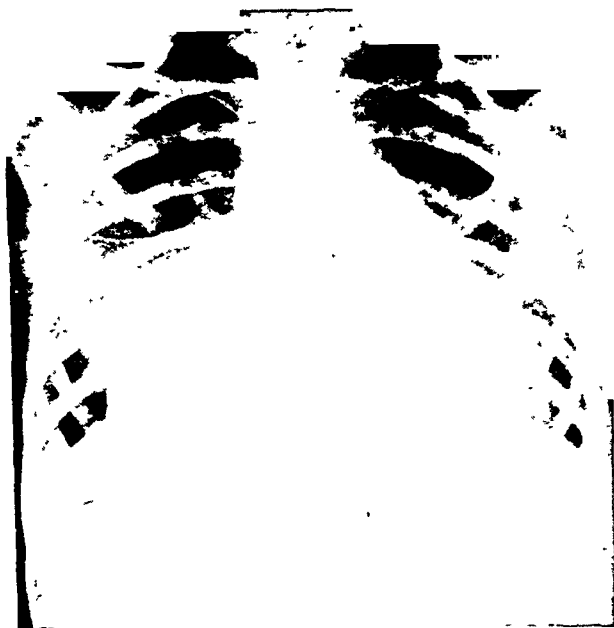


Fig. 2.—M. M. X-ray of the heart taken at the time of discharge showing some reduction in the cardiac-pericardial size. Subsequent fluoroscopy two and one-half weeks later showed the cardiac contour to be normal in size and shape.

DISCUSSION

DR. BERNARD J. WALSH.—When I first saw this patient shortly after her admission to the hospital, I found her lying flat, in no respiratory distress, and with moderate facial pallor. There was no edema or cyanosis of the extremities. The cardiac rhythm was normal. There was no gallop. I was unable to hear any sounds indicative of friction rubs, either pericardial or pleural. No murmurs were heard. The heart sounds were moderately distant. The area of cardiac dulness was considerably increased, extending to about the anterior axillary line in the fourth and fifth left interspaces. There was a flat note on percussion with distant breath sounds over the lower third of the right chest posteriorly. The liver was smooth and slightly tender, and the edge was readily felt three fingerbreadths below the costal margin in the right midclavicular line.

The electrocardiogram (Fig. 3) was within normal range, although there was very slight elevation of the S-T segments in Lead I consistent with acute pericarditis.

Fluoroscopic examination showed a large cardiac-pericardial shadow with very poor to absent pulsations on all borders. The enlargement was chiefly to the left. There was a wedge-shaped density at the cardiohepatic angle on the right, the nature of which was not clear, but it seemed more consistent with fluid in that area than with pneumonic infiltration.

A diagnosis of acute pericarditis with pericardial effusion, cardiac tamponade, and possible myocardial failure was made.

In view of the possibility that some degree of heart failure was present, digitalis was recommended.

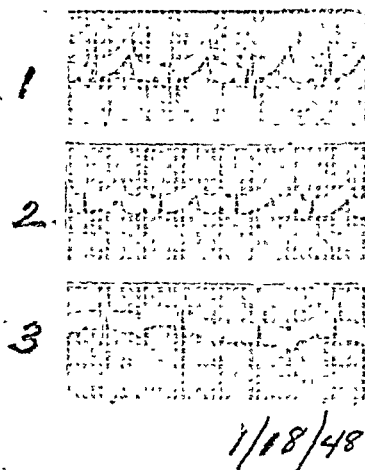


Fig. 3.—Ecg. showing slight elevation of S-T segments and Lead I.

Late on the second hospital day I again saw the patient, and it was apparent that she had grown worse. She was in no particular respiratory distress and was able to lie flat, but she looked much more ill and her facial pallor had increased. The liver had further enlarged. A pericardial tap was done immediately, the needle being inserted in the fifth interspace, approximately 1.5 cm. inside the left border of cardiac dullness. The first 20 c.c. of fluid were light yellow and clear. The remainder of the fluid was dark amber. It was believed that the difference in color resulted from pocketing of the fluid. When about 100 c.c. of fluid had been withdrawn, the patient seemed much improved. When she was returned to her room, it was apparent to all who had seen her before the pericardial tap that she was materially better. Her liver became much less tense and diminished in size by 1.5 to 2 cm.

Pericarditis due to any cause is unusual, both in children and in adults. It is not rare in children, however, this patient being the third we have had in this hospital in the past six months. The cause of the pericarditis, even when there is a good deal of pericardial effusion, remains unknown in the majority of our cases. Pericarditis associated with rheumatic fever makes up approximately 30 per cent of the cases of acute pericarditis we have seen in this hospital. Another 10 per cent of the patients have purulent pericarditis due to the

influenza bacillus, the pneumococcus, or to other organisms. After the diagnosis of pericarditis is made, the next most important decisions concern effusion. If effusion is present, is it causing increasing restriction of the heart? Is it purulent, or not? If there is a leucocyte count of 20,000 or over, and particularly if there is a temperature of 103° F. or more, I believe a purulent pericarditis must be strongly suspected, and it is best to do a pericardial tap. If the effusion is purulent, it is seldom possible to remove the pus except by surgical drainage. If the patient with pericarditis has a large liver and/or orthopnea.



Fig. 4—J. M., 16-month-old child with acute pericarditis with effusion. X-ray of the heart at the time of admission revealed a considerably enlarged cardiac-pericardial shadow. The cardiac size subsequently returned to normal.

even though high fever and considerable leucocytosis are absent, cardiac tamponade can be considered practically certain. It is our practice to observe such patients carefully for increase in the size of the liver and increase in the size of the cardiac-pericardial shadow. If increase is noted by comparison with the first examination, then a pericardial tap is carried out and as much fluid as possible is removed. However, pericardial tap, either because of possible purulent pericarditis or increasing cardiac tamponade, needs to be done only occasionally. In the vast majority of patients, the infection subsides over a period of six or eight weeks, accompanied by steady decrease in the size of the liver and in the amount of fluid in the pericardium.

The x-rays (Fig. 4) show a large cardiac-pericardial shadow in a 16-month-old child who was on the medical service here recently. The second film was taken when the child was ready to leave the hospital. The etiology remains unknown for this patient also. It was not necessary to tap the pericardial sac.

This is the youngest patient I have ever seen with pericarditis. I have seen her recently in the Cardiac Clinic, and she is now well, leading an active normal life. The cardiac-pericardial shadow has returned to normal. The cardiac pulsations are vigorous in all views by fluoroscopic examination.

Addendum.—Feb. 18, 1948: The patient was examined today. She has been eating well and has no complaint. She has seemed to her parents to be quite her usual self. On examination she appeared in good health. The cardiac rhythm, rate, and sounds were normal. The heart sounds were vigorous and loud. There was no edema or cyanosis. There was no enlargement of the liver. Fluoroscopic examination showed a full-sized, normal appearing heart with very vigorous pulsations except in the region of the right auricle.

3. Conference on Actinomycosis, With Pulmonary Involvement

DR. ROBERT C. GARBY.—L. S., a 9-year-old Negro girl, was admitted to Children's Hospital on Dec. 14, 1947, with the chief complaint of a "knot in her throat." Recently she had been fairly well until about ten days prior to entry when she had a cold accompanied by a nonproductive cough and marked malaise, and stayed in bed. The cough was aggravated, and there was some dyspnea while lying flat on her back. Her neck had been stiff for three days, and the night before admission pain was noticed in the neck.

The past history revealed that her first admission to the hospital was on June 29, 1945, for gonorrheal vaginitis, which was treated with penicillin with good results. She was discharged on July 11, 1945, thirteen days after admission. Her next hospital admission was at Gallinger Hospital of this city on Jan. 14, 1946. The diagnosis of left lobar pneumonia was made. She showed marked toxicity during the first week of her hospital stay. The temperature fell by lysis, being normal on the sixth day, and her chest cleared slowly. X-rays showed considerable pneumonic infiltration on the left side. Clubbing of the fingers and toes was noticed at that time.

The next hospital admission was on Aug. 1, 1946, when she had a "knot on left shoulder," had had a cold and cough for several weeks, and her fingers and toes had been swollen for one week. Physical examination at that time showed a firm, fixed, nontender mass protruding from the left chest anteriorly. There was dullness to percussion lateral to the mass and scattered dullness in the left chest posteriorly. Moist râles were heard throughout the left chest with increased breath sounds and scattered râles in the right lung. The fingers and toes were clubbed.

Laboratory examinations revealed a hemoglobin of 12 Gm., with 4.3 million red blood cells and 11,300 white blood cells with 65 per cent neutrophils (58 per cent segmented and 7 per cent stab cells), 3 per cent eosinophils, and 32 per cent lymphocytes. The urine was clear and acid, with a specific gravity of 1.020, albumin 5 mg. per cent, and many white blood cells in clumps.

Repeated blood examinations through August 14 showed a leucocytosis ranging between 11,000 and 17,000 with essentially similar differentials. Repeated urinalyses were essentially negative. No Bence-Jones protein was found. Repeated sputum cultures, concentrated smears, and gastric washings for

tuberculosis were negative. Fluid aspirated from the mass on the chest showed a hemolytic *Staphylococcus aureus* on one culture, and on another examination a fungus was found which the National Institute of Health considered to be a nonpathogen and probably an air contaminant.

Treatment consisted of 20,000 units of penicillin intramuscularly for three days, and again six weeks later 50,000 units of penicillin intramuscularly every three hours were given for forty-eight hours for a return of the gonorrheal vaginitis. The cough gradually cleared over a period of two months, the x-rays cleared somewhat, and she was discharged on Nov. 10, 1946, to be followed as an outpatient.

Her developmental history showed that she did not walk or talk until the age of 2½ years, and her dentition was markedly delayed. Cod liver oil and orange juice intake was believed to have been deficient. For several years she has had epileptoid seizures lasting five to ten minutes during which she "sees" her mother who died of a "nervous breakdown."

Physical examination on the day of her present hospitalization revealed a chronically ill, poorly developed, and poorly nourished child. The temperature was 100.4° F. and respirations 20. There was a tender swelling about the size of a small lime in the suprasternal region, which was fluctuant, moderately fixed, and did not move on swallowing. Congestion of the nasal mucosa was present, and the tonsils were inflamed and hypertrophied. Examination of the lungs revealed increased dullness over the left lower lobe. On deep palpation of the abdomen, slight tenderness in both lower quadrants was present. There was a shallow, indolent-appearing ulcer over the left side of the sternum, surrounded by a dark, leathery discoloration about 3 cm. in diameter. There was marked clubbing of the fingers and toes, as well as cervical, axillary, and inguinal lymphadenopathy.

Laboratory examination of the blood revealed a hemoglobin of 9.5 Gm., 3.9 million red blood cells, 11,500 white blood cells, and 79 per cent neutrophils (72 per cent segmented and 7 per cent stab cells), 1 per cent eosinophils, and 20 per cent lymphocytes. Sedimentation rate (corrected) was 34 mm. per hour. On Dec. 20, 1947, the blood sugar (fasting) was 83 mg. per cent; Kahn and Mazzini tests for syphilis were negative; an ECG was interpreted as being within normal limits.

On Dec. 27, 1947, microscopic examination of material obtained from aspiration of the swelling in the neck was found to be typical of actinomycosis. Biopsy of a left axillary gland was done on Dec. 22, 1947, and was reported as chronic hypertrophy; no actinomycosis was seen. One routine blood culture done here was negative. A blood culture for fungi which was done at the National Institute of Health was negative. Total blood protein shortly after admission averaged about 9 mg. per cent, and the albumin-globulin ratio was reversed, averaging 0.6/1. Gastric washings for actinomycosis have been negative thus far.

A chest x-ray on the day after admission (Fig. 1) was interpreted as follows: "Examination of the chest reveals the cardiac contour to be 'water-bottled' in shape with a loss of the cardiophrenic angles and enlargement to the

right and left of the entire silhouette. This has the appearance of pericardiac effusion with cardiac enlargement. The interlobar fissure is thickened on the right and contains a little fluid, and there is some low-grade infiltration in the lower half of the left lung. Chronic granulomatous disease with cardiac involvement should be ruled out." Four days later another report reads: "Fluoroscopic examination of the chest in the upright, prone, and head-down positions reveals a definite increase in the supracardiac shadow in the head-down position. This represents some pericardial fluid though not enough for pericardial tapping. . . ." On Feb. 6, 1948, the x-ray report reads: "Re-examination of the chest by fluoroscopic and radiographic techniques reveals adequate pulsations of fair amplitude of the heart. . . . There is considerable reduction in the size of the cardiac silhouette. There is some reduction in the amount of infiltration, and at the present time there is some fibrosis and calcification at the roots." The last x-ray report on Feb. 10, 1947, "reveals the cardiac silhouette to be even smaller than at the previous examination. . . ."



Fig. 1.—Actinomycosis of the lung and pericardium.

Sulfadiazine, one gram every four hours, was begun on Dec. 27, 1947, when the diagnosis was established. After the gastric washings were obtained, penicillin, 100,000 units every three hours, was begun on Jan. 7, 1948. On Jan. 12, 1948, many sulfonamide crystals were found in the urine, and sulfadiazine was discontinued and Citra-Sulfa was substituted. High protein diet, whole blood transfusions, intravenous plasma, and supplementary vitamins have completed the therapeutic measures.

During the first month of the patient's hospital stay the temperature ranged irregularly from normal to 100° or 101° F. daily. Since that time it has decreased to a maximum of about 99.8° F. daily (rectal). Objectively and subjectively there has been marked improvement with considerable increase in strength, brightening of the mental picture, and disappearance of the cough. The suprasternal abscess ruptured on Dec. 18, 1947, drained for about two weeks, and then closed and has remained closed. The chest lesion has apparently healed completely, leaving considerable scar formation.

Follow-up Note, Feb. 29, 1948.—Clinically this child continues to show vast improvement and response to treatment. This is reflected by the chest film (Fig. 3). She still continues to evidence a low-grade fever, however, with a temperature of about 100° F.

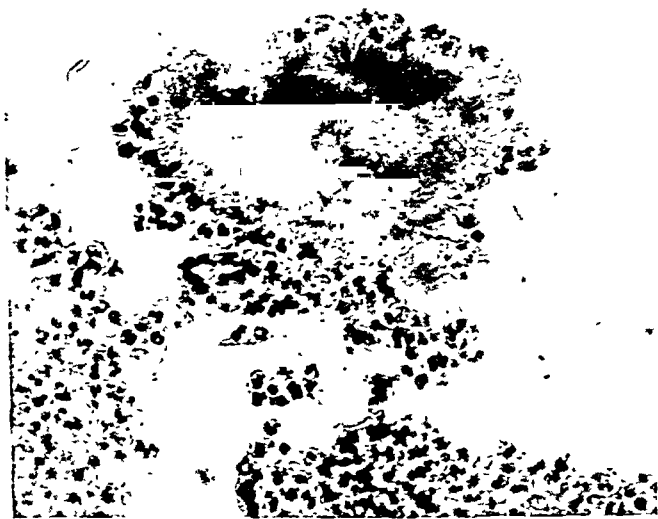


Fig. 2.—L. S. Microscopic section revealing the typical sulphur granules of mycelial growth characteristic of *A. bovis*.

DISCUSSION

DR. THOMAS BRADLEY.—This case illustrates several characteristic features of actinomycotic infections of the lungs and chest wall. First, there is evidence that the lesion is of quite long duration. In June of 1945 the child was admitted to Children's Hospital with gonorrheal vaginitis, at which time it was noted that there were coarse ronchi during inspiration. There was no clubbing of the fingers at that time. She was given oral penicillin in doses of 20,000 units every three hours for ten days. It is not unreasonable to suppose that the fungous infection was present at that time and that it was possibly affected by the treatment. About six months later she was treated in Gallinger Hospital for lobar pneumonia with sulfathiazole, and at that time clubbing of the fingers

was noted. She was discharged from Gallinger Hospital after twenty-three days of treatment with residual changes in the base of the left lung which were thought to be due to pneumonia. She was again admitted to Children's Hospital in August of 1946 with a definite suspicion that actinomycosis was the cause of the persistent lung pathology, but a careful search for the fungus was unsuccessful. Poppe reports that in nineteen cases seen at the Barnes Hospital the diagnosis was not made in several cases until two or three years of intermittent study had been made.

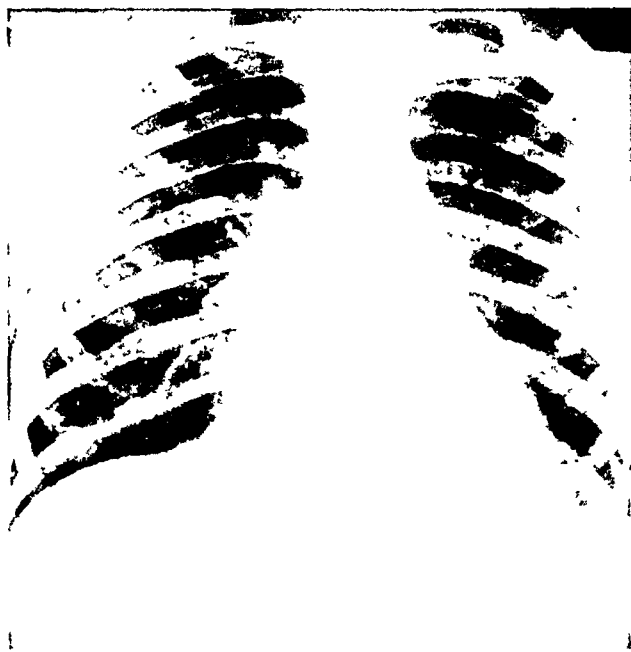


Fig. 3.—Actinomycosis showing marked clearing from the parenchyma and pericardium. There is still considerable fibrosis at the roots.

The advent of chemotherapy has brightened the outlook in actinomycotic infections, but it must be remembered that patients recovered in some instances prior to the use of these drugs. In 1911, Harbitz reported eighty-seven cases of actinomycosis involving the thorax and lungs with 100 per cent mortality. In 1930, Good of the Mayo Clinic reported that this type of infection was almost uniformly fatal. Two years later, Wangenstein commented on the fact that all cured patients except one had had some form of surgery, such as rib resection, drainage of abscesses, and thoracoplasty.

Poppe reports on nineteen patients seen in the Barnes Hospital over a period of years, in seven of whom the disease was apparently arrested. In these seven patients some type of rather radical surgery was used in conjunction with either x-ray, thymol, penicillin, or the sulfonamides. Iodide therapy was not used in these cases.

Apparent cures have been reported from a variety of medications, and it is probably true that the situation is somewhat analogous to the treatment of pulmonary tuberculosis. Proper combinations of surgery to drain secondarily infected abscesses with chemotherapy offer good results if the patient is seen early enough.

Just which drug is best is not completely clear, but the best results have been obtained recently with penicillin, or with a combination of penicillin and sulfonamides. Abrahams and Miller report that penicillin has a greater inhibitory effect in in vitro experiments than sulfathiazole or sulfadiazine. Strains of *Actinomyces israeli* recovered from human subjects were grown in glucose nutrient agar containing varying concentrations of sulfathiazole and sulfadiazine. Some growth-inhibitory effect was noted in levels of from 10 to 20 mg. per cent, but the effect was thought to be too slight for much therapeutic use. On the other hand, penicillin definitely inhibited growth in levels of 0.1 and 0.2 unit per milliliter of medium. This level is within therapeutic range in human beings.

Since actinomycosis is a disease characterized by long latent periods, followed by recrudescence, it is justifiable to state that several years should elapse before the disease is called cured rather than arrested.

To sum up the attitude of most clinics at the present, the following can be said:

1. Pulmonary actinomycosis with involvement of the chest wall is no longer to be considered a hopeless disease.
2. Therapy should consist of a varied attack. Abscesses should be adequately drained; rest for the patient and for the involved area in particular should be utilized.
3. Some patients will respond to internal medication alone, but this should not be relied upon to violate established surgical principles. The medical and surgical treatment of tuberculosis is analogous.
4. At the present, penicillin probably offers the best chance for cure. The simultaneous use of sulfadiazine helps with secondary invaders which may be resistant to penicillin.

DR. CHESTER W. EMMONS.*—I have seen this patient only once before and have little to add to the discussion. The diagnosis of actinomycosis in this patient rests upon the demonstration of actinomyceotic granules from one specimen obtained by aspiration of one of the subcutaneous lesions. I saw the section of this material only under a moderate magnification, and while it appears to me to be typical of actinomycosis, I should like an opportunity to examine a Gram-stained section with an oil immersion lens to rule out the possibility that this is a granule of, for example, staphylococcic actinophytosis (botryomycosis). However, this has no doubt been done in the hospital laboratory.

It would be helpful in confirmation of the diagnosis if cultures could be isolated. Since the lesions were not draining and sputum was not available when I saw the patient a week ago, we made cultures from the venous blood on

*Principal mycologist, National Institute of Health.

the improbable chance that there had been a hematogenous spread and that actinomyces still might be present in the circulating blood. This occurs in rare cases, but the cultures in this case have remained sterile.

I think that the clinical course in this patient has not been typical of actinomycosis. If the patient has had pulmonary actinomycosis since the onset of the present illness, it would be expected that a draining sinus tract would have developed through the thoracic wall. I understood that there was no x-ray evidence of continuity between the pulmonary lesion and the substernal abscess, although x-rays were taken during and at the height of development of the latter. Both the subcutaneous lesions have ceased to drain now. Is it possible that these lesions followed hematogenous or lymphatic dissemination from a transitory maxillary lesion? It would be desirable to continue attempts to obtain sputum, and to study additional gastric washings in order to shed more light on the nature of the pulmonary lesions.

Since pulmonary actinomycosis has such a grave prognosis, it is surprising to see this patient in her present condition. Therapy so far has not been directed toward actinomycosis, as I understand, and penicillin and other drugs she has received in the past have not been given in sufficient amounts and over long enough periods of time so that a response would be expected in actinomycosis. It may be, however, that the penicillin she has received has been of some benefit, and since several reports during the past three years have indicated that actinomycosis responds to penicillin therapy, its continued use in this case seems justified.

DR. E. CLARENCE RICE.—The aspirated material from the fluctuant mass was smeared and cultured, and no mycelial elements were found. It was only after some of the material was placed in formalin and paraffin sections prepared that the typical granules of mycelial growth were found (Fig. 2). These are the typical "sulphur granules" seen in infections due to *Actinomyces bovis*.

This is the second case of actinomycosis which we have had at Children's Hospital. In the other patient the actinomyces were found in a biopsied specimen.

On a number of occasions we have found similar bodies in the crypts of removed tonsils when sections were examined microscopically. This apparently is not an uncommon finding, and these bacteria are probably saprophytes.

4. Conference on Acute Regional Enteritis

DR. GEORGE WILLIAM WARE.—D. D., an 8-year-old white boy, was admitted to Children's Hospital, on the service of Dr. William O'Donnell, on November 24 complaining of a sore throat. Two weeks previously a diagnosis of scarlet fever had been made, for which sulfadiazine and later penicillin were given. A papular rash appeared a week before admission and persisted.

Family history and past history were negative except for a pyloroplasty at the age of one month.

Physical examination upon admission revealed a young boy who was acutely ill and in obvious discomfort. The buccal and pharyngeal membranes were

fiery red in appearance. The right tonsil was covered with an exudate. A papular rash was present over the extensor surfaces of both arms and legs and the entire face, and was noted to blanch on pressure. The remainder of the physical examination including the abdomen was negative. Urinalysis revealed 15 mg. of albumin, a trace of acetone, and on microscopic examination there were a few white blood cells with clumps. The red blood count was 3.6 million with 9.5 Gm. of hemoglobin. The white count was 12,300 with 80 per cent neutrophils, of which 64 per cent were segmented forms, 14 per cent band forms, and 2 per cent young forms. There were 16 per cent lymphocytes, 2 per cent eosinophiles and 2 per cent basophiles.

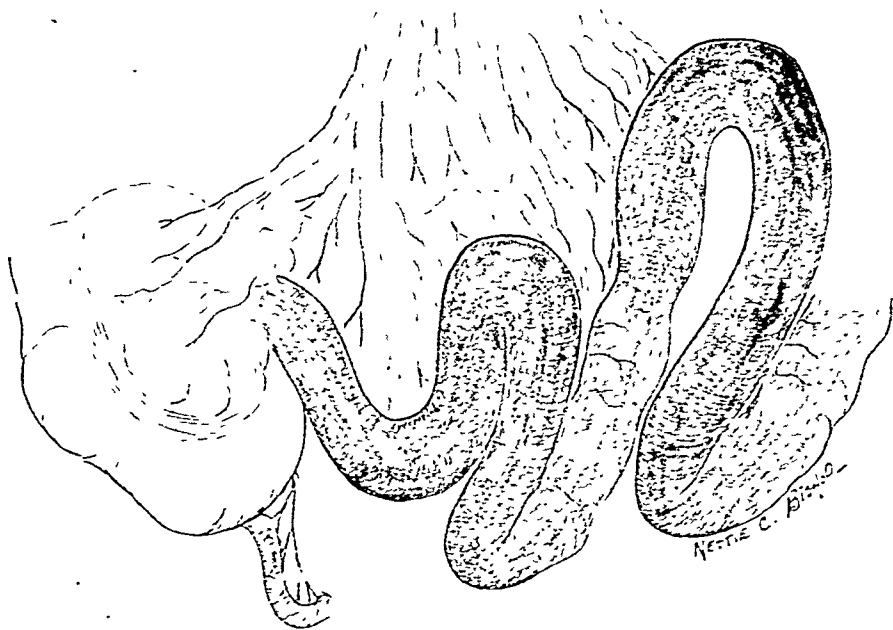


Fig. 1.—Illustration showing the area of inflamed ileum proximal to its junction with the cecum.

Penicillin therapy, 100,000 units every three hours, was immediately instituted and supplemented by the use of Elixir Benadryl. On the following day the temperature was 104° F. and pulse 120. The rash seemed to have improved somewhat. On the second hospital day the improvement continued, and the patient was placed on a soft diet. That evening he complained of abdominal pain of a generalized nature, which gradually increased in severity during the subsequent twenty-four hours. On the fourth day of hospitalization, the child commenced to vomit and had six watery bowel movements. The abdominal pain continued, and moderate diffuse abdominal rigidity with some distention became evident. The white blood cell count was now 13,700. The differential count showed 79 per cent neutrophils (73 per cent segmented and 6 per cent band forms), 19 per cent lymphocytes, and 2 per cent eosinophiles.

The patient was seen in surgical consultation by Dr. Robert Coffey, and a diagnosis of ruptured appendix with diffuse peritonitis was made and an immediate operation advised. Preoperatively, 250 c.c. Hartmann's solution containing 5 per cent glucose were given intravenously.

Under nitrous-oxide ether anesthesia, a lower right rectus incision was made. On entering the peritoneal cavity, a strikingly large amount of free serosanguineous fluid was encountered, 750 c.c. being aspirated. The small bowel, beginning in the distal jejunum and terminating abruptly at the ileocecal valve, was of a fiery red color, slightly edematous, and the mesenteric nodes of the involved area were slightly but not notably enlarged (Fig. 1). The mesentery of the involved bowel was not appreciably thickened, and its vascularity did not appear abnormal. The cecum and appendix were not involved. After deciding against the removal of the appendix, the incision was closed in layers without drainage. Immediately after the termination of the operation the patient was given 250 c.c. of whole blood intravenously.

The postoperative course was relatively uneventful. On the second postoperative day, urticarial wheals were observed on the upper extremities and over the abdomen, and the patient complained of severe itching in these areas. Rather prompt relief was secured by the use of benadryl. The white blood count at that time was 9,400 with a normal differential count. The platelet count was 244,000 per cubic centimeter. The patient was discharged from the hospital on the seventh postoperative day.

During the three-month period since the patient's discharge from the hospital he has recuperated completely, a weight gain of 4 pounds has occurred, and he has no complaints referable to the gastrointestinal tract.

DISCUSSION

DR. ROBERT J. COFFEY.—Since the original description by Crohn and his associates¹ in 1932 of chronic regional enteritis, much has been learned about the clinical manifestations, course, and prognosis of this disease. It is essentially a disease of youth, involving in its chronic form any part of the jejunum, ileum, or right colon in a cicatrizing granulomatous process with a decided tendency toward the formation of internal and external fistulas. This chronic form of the disease is the one most frequently encountered and has been studied thoroughly. The acute manifestations of the disease, on the other hand, have seldom been studied pathologically since resection at this stage is seldom attempted. That such acute manifestations of the disease bearing his name did occur was well recognized by Crohn, and since then numerous cases have been reported. Erb and Farmer² pointed out that the occurrence of hemorrhagic edema of the ileum with conspicuous regional lymphadenopathy represents an early phase of regional enteritis and is characterized clinically by its similarity to acute appendicitis.

Whether all such cases of acute enteritis represent an early stage of chronic regional enteritis is a debatable point. Because of the occurrence of a rash preoperatively and the development of urticaria postoperatively, an intestinal anaphylactoid or allergic reaction was considered when the markedly hemor-

rhagic condition of the involved bowel with serosanguineous peritoneal fluid was observed. However, the sharply segmented area of involvement pointed to a true regional enteritis.

It has been suggested that true acute regional ileitis may be distinguished from nonspecific acute enteritis by the absence of enlarged mesenteric lymph glands in the latter.³ However, since so little is known concerning the etiology and pathogenesis of acute regional enteritis, it seems illogical to apply any such criterion. Usually the involved bowel is reddened, thickened, and edematous, and the glands are conspicuously enlarged. Free peritoneal fluid is generally present and may be serous or serosanguineous. Cultures of this peritoneal fluid and of the involved mesenteric glands have been consistently negative. The terminal ileum is usually the site of maximal involvement, while other areas in the jejunum, proximal ileum, or right colon may be affected in continuity or in a patchy manner.

Prior to Crohn's work, the acute form of this disease had been seldom described, and the chronic manifestations were usually considered to be tuberculous. This latter etiological factor has been definitely excluded as a result of many studies.⁴ The similarity of the pathologic manifestations in this condition to those found in Boeck's sarcoid have been interpreted as indicating a possible etiological relationship. Erskine⁵ has observed the association of acute appendicitis and acute terminal ileitis in several instances and is of the opinion that both may be due to primary involvement of the mesenteric lymph nodes. This is in keeping with the experimental work of Reichert and Mathes,⁶ who were able to produce somewhat similar lesions in experimental animals by the injection of sclerosing solutions into the mesenteric lymphatics. However, subsequent investigators failed to substantiate these results.⁷

Since in its chronic form this disease occurs in early adult life, it is probable that the acute manifestations of the disease will be encountered in childhood and youth. Rose³ refers to acute cases of the disease occurring in children of the ages of 5, 6, and 10. In the series of Fallis,⁸ the youngest patient in whom the chronic disease was identified was 9 years old. Koop and his associates⁹ have recently reported a case of the chronic form of the disease in a newborn infant in whom the pathologic examination of the involved bowel revealed the typical changes of chronic regional enteritis.

The most important consideration in acute regional enteritis is the prognosis. Crohn¹⁰ encountered eleven patients with the disease, of whom eight did poorly, six being eventually operated upon. However, most of the other reports have been less pessimistic in regard to the outcome.^{3, 11, 12} Smithy¹³ feels that a spontaneous cure follows in most acute cases and that progression to the chronic form of the disease seldom ensues. A true picture of the ultimate outcome of these cases, however, depends on long and careful follow-up studies.

It is generally agreed at this time that in the chronic form of the disease a sidetracking operation, either with or without resection of the involved bowel, is necessary. There is similar agreement that conservatism should be employed when acute regional enteritis is encountered. Inasmuch as the majority of patients with the acute form are operated on under an erroneous diagnosis of

acute appendicitis, the disease is identified on entering the peritoneal cavity. Since a spontaneous cure may be anticipated in the majority of early cases, surgical extirpation of the acutely inflamed bowel or a sidetracking operation is unwarranted. Removal of the appendix may eventuate in the development of a fecal fistula, a fact pointed out in a series studied by Coffey.¹⁴ Mixter¹⁵ and Fallis⁸ advise against appendectomy, and certainly this procedure is undesirable if the cecum is involved.

The subsequent management of acute regional enteritis involves careful periodic observations plus recourse to roentgenologic study of the gastrointestinal tract in the event that suspicious signs or symptoms develop. It is our feeling that the use of intestinal chemotherapeutic agents such as succinyl-sulfathiazole or oral streptomycin is warranted for a month or six weeks following the identification of the acute disease.

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Psychologic Aspects of Pediatrics

SPECIFIC READING DISABILITY

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THERE is a sizeable group of children whose ability to read is well below their potentiality for learning in general as measured by clinical observation and intelligence tests. It is estimated that between 10 and 15 per cent of children in American schools are unable to read at their proper school grade level and yet are able to perform adequately in academic fields which do not require reading. At one time these children were considered stupid, careless, or lazy. Though a number of different conditions contribute to the disability, there is reason to believe that the large majority of afflicted children have a specific defect, probably residing in the central mechanisms governing the language functions, which manifests itself by difficulty in understanding the written word.

The effect of reading disability on the emotional status of the child and on his future emotional and mental development may be profound; and this is especially unfortunate since the condition is remediable. Responsibility for recognizing a reading defect rests primarily on the school. Unfortunately many schools are lax in this respect. It is, therefore, advisable that the physician, in taking histories on children of school age, make inquiries regarding performance at school and investigate difficulties if they are present.

SYMPTOMATOLOGY

Specific reading disability is a syndrome characterized by (1) difficulty in comprehending written language. Associated with this are (2) alterations in lateral dominance, (3) disturbances in speech, and (4) unusual clumsiness. A further characteristic of the clinical picture is (5) the frequency with which language difficulties and alterations in lateral dominance are observed in other members of the family. (6) Emotional disturbances, arising out of the subjects' inability to read, are generally present.

Specific reading disability is sometimes referred to as strephosymbolia, meaning "twisted symbols," as dyslexia, and as developmental alexia. Orton¹ objects to the designation "congenital word-blindness," originally introduced by Morgan,² since the condition is not congenital and there is no blindness.

1. The clinical picture presented by the poor reader is fairly uniform. The child has been considered bright—often unusually so—until he enters school. He may have enjoyed being read to and have shown normal interest in numbers and letters. No problem of any sort was evident. During the first two years in school he does not learn to read. Since much of the reading at this level depends on memorizing, the nature of the defect may not be apparent

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until later. If the child goes to a "progressive" school where there is no insistence on reading until the pupil shows a spontaneous interest, the disability may remain unrecognized for three or four years.

At first, only reading and spelling are difficult. There is often reversal of letters, syllables, and whole words. More commonly, individual letters are written backward and sometimes even upside down. The letters "b" and "d" are frequently confused, as are "p" and "q." Words such as "was" and "saw," "on" and "no," are stumbling blocks, and there may be confusion between words like "from" and "form," and "calm" and "clam." In rare instances the child can read only from right to left (mirror reading). This is sometimes associated with mirror writing. The handwriting may be poor, but usually copying is done accurately and neatly. The learning of geography and history are affected, for the child cannot read his assignments. Grades in arithmetic are usually good. Occasionally there is a reversal of digits, as, for example, reading 42 for 24. Later, performance in arithmetic is also affected as the child is unable to read the written problems and cannot follow the directions. The results on written examinations are poor as is all written work. On the other hand, the child may surprise his teachers by his intelligent responses in class discussions and recitations.

2. Alterations in lateral dominance, particularly ambidexterity and mixed dominance, as right-handedness and left-eyedness or left-footedness, are common in children with reading disability. In a careful study of twenty-two subjects, Eustis³ found that only four were entirely right-handed, eighteen were ambidextrous, and none was left-handed. A high proportion of left-eyedness, amphiocularity (sighting with either eye), and crossed laterality was found in the same group.

3. Speech disturbances are frequently associated with specific reading disability. They were present in about half of the patients studied by Eustis.³ There may be delay in the age of starting to talk, impure speech or lisp, stuttering or cluttering speech.

4. A considerable proportion of affected children are abnormally clumsy (developmental apraxia or developmental awkwardness). Their movements are jerky, uncoordinated, and bungling, and resemble those of the rapidly growing adolescent who has not yet become accustomed to the changes in his body size and proportions. The condition is evident in early childhood but becomes more prominent during the school years when the child starts to write and participate in games. Presumably the basis for this is mixed dominance. In such instances the child, instead of being able to use both hands with equal skill (ambidexterity), uses both hands equally awkwardly (ambilevosity).

5. That specific reading disability probably has a hereditary basis is indicated by the high incidence of alterations in lateral dominance, speech disturbances, and reading difficulties in other members of the family.

6. Children with this defect are usually anxious and unhappy because they are unable to do their school work as well as their peers. Conscious of their disability and ridiculed by the other children for their mistakes, they approach

reading with the expectation of failure. They consider themselves stupid and inferior, and they may refuse to try to read or even to pay attention in school. They are often restless, hyperactive, and easily distractible. Parental dissatisfaction with school performance and pressure for better work intensify their anxiety, and these emotional factors further interfere with learning.

The child with a reading disability often shows unusual interest in drawing, mechanics, and athletics. He derives pleasure in a normal way from listening to stories and discussions and from conversation.

Specific reading disability, like other difficulties in the language functions, is much more common in boys than in girls. It is estimated that boys are afflicted from three to four times as often as girls.

The age at which specific reading disability is first recognized depends on the teacher's understanding of the difficulty and the alertness and concern of the parents. The usual age is 8 to 14 years. It can however be recognized earlier before the formal teaching of reading is begun if the possibility of a defect is entertained in children with a history of speech difficulty, alterations in lateral dominance, and other instances of disturbances in the language functions in the family.

Gillingham and Stillman⁴ describe a number of tests for reading disability which can be used in young children. The tests are designed to measure the child's ability to recall sequences. A row of pictures of familiar objects is presented to the child, and he is then asked to name them. The order in which he recalls the pictures, whether from left to right or right to left or in a haphazard fashion, is noted. Similarly, a row of toy animals is shown. The animals are covered, and the child is asked to arrange a duplicate set in the same order. The examiner starts with three animals and increases the number, one at a time, until the subject shows confusion.

Again, the child is shown a simple drawing, for example, the profile outline sketch of a chair. His attention is distracted for a few moments, and he is then asked to draw the now concealed figure. This is done fifteen or twenty times. Note is made as to whether the figures are reversed or so confused as to be unrecognizable.

A further test is for auditory confusion. The child is asked to repeat detached syllables, and the frequency of reversals is observed.

ETIOLOGY

According to Orton,¹ the basis for specific reading disability is a faulty establishment of dominance in the reading centers of the brain. The process of reading, as well as speaking and writing, is controlled or initiated or overseen largely, if not entirely, from one hemisphere of the brain. Any defect in the dominant half of the brain, however produced, is likely to result in extensive damage to the language functions, while injury to the corresponding area in the other half of the brain generally gives no specific language symptoms whatsoever. The brain hemisphere which has major control over the language functions is also the

hemisphere which controls handedness, eyedness, and footedness. Although there are exceptions, it is the rule that in right-handed people the left hemisphere of the brain is the dominant one, and vice versa.

Persons with a specific defect in reading are usually able to see and to interpret objects correctly. It is only in the complex function of word recognition that any obstacle is encountered. The difficulty is not one of vision but of comprehension.

Eustis³ subscribes, in the main, to the thesis of Orton. He looks upon specific reading disability as a familial syndrome associated with ambidexterity and speech defects. He would separate poor readers of this type from the children who fail to read for a multiplicity of other reasons—physical, mental, emotional, educational, and social.

The nature of the disturbance in the cerebral mechanisms which regulate recognition of the written word is not clear. There are no demonstrable organic changes in the brain. Orton¹ offers as an explanation a "faulty establishment of dominance in the reading centers of the brain." It is conceivable that, in a certain number of cases, there may be simply a retardation in development similar to what occurs in children who are slow in beginning to talk. There is variability in all biologic attributes. Children vary in the age at which they are ready to sit up, stand, walk, be toilet-trained, etc., just as they vary in body size, body proportions, and facial features. The age at which children are ready to learn to speak differs widely. Whereas the use of words ordinarily begins in the first half of the second year of life, there is a fairly large number of mentally normal children who are unable to talk until they have passed their third birthday. Similarly, most children of normal intelligence are ready to learn to read at 6 years. In a certain proportion, the age of readiness may be much later, but these children ultimately catch up with the average child and learn to read normally, in much the same manner as children who begin to speak late. Unfortunately in the case of reading the interference of parents and teachers and the child's own feelings of inadequacy introduce emotional factors which interfere with learning.

Emotional Factors.—Children who are unable to read are almost invariably emotionally disturbed. Indeed there are some who believe that the personality disturbance is the paramount and central factor and that emotional difficulties antedate the disorder.⁵ The child who is expected to read before he is developmentally ready is in the same position as the child who is expected to respond to any other training procedures before he is ready. The parents are disappointed with the child's performance, and they exert pressure for better work. The child is frustrated by his inability to live up to parental expectations and is discouraged by the criticisms of his parents and teachers and by his failure to keep pace with his fellow students. Any attempt at reading is approached with anxiety, and the child comes to feel stupid and inadequate. He may react with an assumed indifference, with bravado, with hypermotility and distractibility, or with dejection.

Method of Training for Reading.—One reason for the increased frequency of specific reading disability is the use of the "sight" method for teaching chil-

dren to read instead of the "phonic" method. By the older phonic method, children were taught the sounds as well as the forms of the individual letters. By the newer sight method, the children are expected to grasp the meanings of whole words. The normal child learns to read more quickly by the new method, but the child with a reading disability is at a great disadvantage. The greater frequency of reading disability in America has been attributed to the widespread use here of the sight method. The condition is much less common in Germany, where the phonic method is used and where, in addition, the phonetic spelling is more rational.

Training for Handedness.—It is possible that the custom of encouraging the ambidextrous child to use both his hands as he pleases is a factor increasing the incidence of specific reading disability.

Opinions differ as to whether choice of the dominant hand determines the side of the brain which will lead and which will contain the language centers, or whether brain localization is the determining factor. Nielson⁶ states that "brainedness comes first." He attributes the occasional instances of right-brainedness in right-handed persons to a shift from natural left-handedness to right-handedness. However, this fails to explain the occasional occurrence of ipsilaterality of handedness and brainedness in left-handed persons, since this would necessitate the training of a naturally right-handed person to the use of his left hand.

Nielson prefers the terms major and minor to the usual designations of dominant and recessive when applied to the hemispheres of the brain. Though the hemisphere which is to lead is hereditarily determined, there is no essential difference between the functional capacity of the two hemispheres at birth. It is for this reason that, in cases of severe trauma to the major hemisphere early in life, the minor hemisphere invariably takes over the function of the major.

Phelps,⁷ in discussing the management of the child with hemiplegia, urges that when the dominant hand is handicapped, no exercise whatsoever should be given to it. He believes that manipulation of the affected limb interferes with the development of cerebral dominance on the uninjured side of the brain. In his experience, mental retardation, speech difficulties, seizures, and behavior disorders of all types are much more common in children with right hemiplegia than in those with left. He advises against treatment of the affected arm unless one is perfectly sure that it is not the dominant one.

Contrary to the opinion of most neurologists, Blau⁸ contends that cerebral dominance is determined culturally. The potentiality for one or the other cerebral hemisphere to lead is an inherent human property, but the choice of which side is to lead depends on the experience of the individual. Early handedness sets the location of the cerebral language centers.

It would appear from these differing views that, whether or not it is the rule that handedness determines cerebral dominance or vice versa, the choice of the master hand by the young child can, under certain circumstances, determine which side of the brain will lead. It seems reasonable, therefore, to encourage the use of one or the other hand in children who appear to use both hands with equal or nearly equal dexterity, so that cerebral dominance will

be established in one or the other cerebral hemisphere. Orton¹ advises that in the group of children who are not developing a selective skill in either hand or in whom the balance is close, the skill and habit of use of the hand which has the greater capacity be increased. The so-called ambidextrous person is usually a native sinistral who has acquired a considerable measure of skill in certain right-sided activities. In many instances there is no apparent harm from training on the two sides, but it seems likely that even the very skillful ambidextrous individual would have been more facile had he been trained electively in accordance with his natural bent.

DIFFERENTIAL DIAGNOSIS

Specific reading disability should be suspected when a child is not doing as well in school as one would anticipate from his general intelligence, especially when the difficulty relates specifically to reading and spelling. Other diagnostic possibilities are mental retardation, ocular or auditory defects, and emotional blocks. The diagnosis is established by psychologic tests which show a discrepancy between performance on a general intelligence test and on a reading test.

Visual Defects.—Visual defects account for a certain proportion of poor readers. Romaine⁸ lists the ocular blocks in reading disability under five headings: (1) general physical disabilities having ocular manifestations; (2) diseases of the eye; (3) errors of refraction; (4) motor anomalies of the eye; and (5) aniseikonia, a condition in which the ocular image received by one eye differs in size and shape from that seen by the other.

Any severe, general, lasting illness may lead to rapid tiring of the eyes with loss of ability to accommodate for reading. With fatigue of accommodation there is often loss of power of convergence, which is essential for simple binocular vision.

With errors of refraction the child gets a blurred image and is unable to distinguish the printed letters. Reading is slow, there are many mistakes, and comprehension is poor.

Defects in the coordination of the two eyes and in eye muscle balance are found occasionally in children who read poorly. For normal binocular vision, both eyes should focus on the object, and the two images should be fused in the brain. When fusion is incomplete, the images perceived by the two eyes overlap or one is seen above the other, and this will necessarily cause considerable confusion in reading.

When the visual images received by the two eyes are of different size (aniseikonia), there may be a definite block to normal functioning of the eyes. Romaine⁸ has observed improvement in a relatively large percentage of patients with reading disability after this condition has been corrected with lenses.

Park⁹ reviewed the ocular findings in 133 children with dyslexia. A fourth of the children were ametropic. Abnormal motility was rare. The incidence of extremely weak or absent stereopsis (vision for depth) was high (22 per cent). Almost half of the children were heterophoric. Though fusion ability was present in practically all the children, Park found that weak fusion amplitude,

especially weak recovery ability from dyslopia, was definitely associated with dyslexia. As a consequence, an unusual amount of nervous energy is required to adjust the foveal positions constantly in order to achieve a single image.

Sensitiveness to visual defects varies widely in different individuals. Some are aware of the slightest defect; others may carry a severe defect for a lifetime without complaint. A person carrying a visual defect without symptoms may become aware of his limitation only when the general health weakens and the load becomes greater than can be handled.

Children rarely complain of ocular symptoms. Unable to localize their difficulties, they simply refuse to read, and, in time, psychologic blocks are added to their ocular disabilities.

Defective Hearing.—Defective hearing may delay the child in learning to read. This is a greater handicap when the auditory or phonic method is used in training than with the sight method. The child hears blurred or indistinct sounds, is unable to associate them with the words being read, and cannot recognize them later. When there is only partial deafness, this may be entirely missed until the child enters school. Deafness should be suspected if the child constantly asks for repetition of directions.

The usual tests for hearing will disclose most hearing defects. The audiometer is useful in detecting the rare cases of regional deafness where the deafness affects mainly the tone range covered by human speech. It will also reveal cases of developmental word deafness where there is difficulty in recognition of the spoken word. In these children the audiometer gives a normal picture.

PROGNOSIS

The large majority of poor readers who receive ordinary educational opportunities sooner or later learn to read as well as others, and many achieve positions of eminence in academic fields. It is possible that the defect persists, but with increased intelligence and experience, the subjects make adjustments which permit them to read normally. However, improvement can be hastened by proper training, and, in this way, much unhappiness can be avoided. Moreover, a small proportion of poor readers never learn to read unless they receive special training. From conversations with adults who have been poor readers during childhood it seems likely that, in a certain number of individuals, the defect is outgrown in much the same way as impurities in speech, which are so common in children, are mastered later on.

MANAGEMENT

The parents of the child with a reading disability should have some understanding of the nature of the defect. They should know that the child's failure is not due to any fault of his own. Comparisons with siblings and other individuals should be avoided and pressure for better work discontinued. Every effort should be made to restore the child's self-confidence.

Defects in hearing and in vision should be corrected as far as possible. Orthoptic training or exercise of the eye muscles improves poor fusion due to muscle weakness and is beneficial in these cases.

Remedial work should be undertaken only by a teacher familiar with the field.¹⁰ Improvement is related to the pupil's willingness to learn, and it is sometimes weeks or months before the emotional blocking can be broken down sufficiently so that the child is willing to try to read. Thereafter progress is rapid. Instruction should start at the child's reading level, but the content should be interesting and suited to his age. Only harm can be done by presenting a 10-year-old with primers or the usual first-grade readers, no matter how poor his ability.

There are at least three approaches to the teaching of reading: the visual, the auditory, and the kinesthetic. All should be used in remedial work. Through the visual method the pupil is taught to perceive the general shape of words, whether they are long or short, tall or low. In this way he learns to distinguish words from one another in the same way as he distinguishes pictures of a house and a chair, etc. The first letter also gives a clue to the word and, similarly, word endings help.

The auditory or phonic technique consists of teaching the child to analyze and recognize certain familiar units by their sounds. Thus "black," "blue," and "bloom" all have the familiar "bl" sound, and "Jill," "hill," and "fill" all rhyme. By this method larger words are broken down into small units. The kinesthetic or motor discrimination method means tracing words, copying letters in their proper sequence, feeling block letters, and feeling the position of the tongue and the lips while pronouncing words. This valuable technique is often neglected.

By analyzing the pupil's errors, the trained teacher will be able to formulate the most suitable pedagogic approach. A proper remedial program will stress the phases of reading in which the pupil is deficient but should, at the same time, include other training methods.

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Comments on Current Literature

MEGALOBlastic ANEMIA

THE January, 1948, issue of *Blood* is devoted in its entirety to megaloblastic anemia, with special emphasis on pernicious anemia. These articles are the first of a series of some eighty articles to be published in honor of Dr. George R. Minot. One article of the current series, "Pernicious Anemia From Addison to Folic Acid," by Russell L. Haden¹ is an excellent review, which gives the historical highlights from the time of Addison to the discovery of folic acid. Haden points out that it was the work of Castle which furnished the final proof that pernicious anemia is a deficiency disease dependent primarily on a gastric defect. This author summarizes the various methods of therapy, stating that while many attempts had been made through the years, no single specific substance, responsible for the beneficial effect, had been isolated. Meanwhile folic acid, a single chemical substance, present in liver, yeast, spinach, and grasses, was shown to be effective to some degree in macrocytic anemias.

In a discussion of "Pernicious Anemia, Nutritional Macrocytic Anemia, and Tropical Sprue" Lucy Wills² reviews the entire subject, and stresses the point that a single symptom complex, such as that of a macrocytic hyperchromic anemia, may be a part of many different disease entities. Of particular interest to the pediatrician are the comments on nutritional macrocytic anemia. While Dr. Wills, working in India, had not seen a case in a young child, she refers to the reports of Giglioli³ in 1934, in which six out of fifty-one patients described were below the age of 12 years, the youngest being 11 months old. In a discussion of treatment, Wills states that until the hemopoietic activity of folic acid was discovered and its conjugated forms gave workers a chemically pure active component, no pure substance with similar activity was available. However, she emphasizes the fact that while folic acid has brought about remarkable hemopoietic responses in all three forms of anemia (pernicious, nutritional macrocytic, and tropical sprue), in general completely normal blood levels have not been restored.

Recently Zuelzer, Newhall, and Hutaff⁴ have described megaloblastic anemia of infancy which is characterized by changes in the blood and bone marrow resembling those of Addisonian pernicious anemia, and which showed specific response to folic acid. Fifteen patients ranging in age from 5 weeks to one year were studied. Eleven of the fifteen had histamine-resistant achlorhydria, and macrocytic anemia of varying degree was present in all cases. Hemoglobin levels on admission ranged from 1.7 to 8.3 Gm. per 100 ml. Folic acid was administered by intramuscular injection in all except two instances, the daily dosage varying from 10 to 100 mg., and the total dosage, from 50 to 900 mg. The average course of treatment consisted of two daily injections of 10 mg. over a period of one week. To two patients folic acid was given by mouth in daily doses of 5 mg. for a ten-day period. In every case a characteristic increase in reticulocytes, up to 23 per cent, took place about the fifth day after initiation of therapy. Red cell counts and hemoglobin levels rose significantly. Careful bone marrow studies revealed that in response to folic acid therapy, most of the significant changes took place during the first five days after treatment.

The progression of marrow changes in such an early response to folic acid is summarized by Zuelzer and his associates as follows: "The megaloblasts lose their characteristic structure, and in twelve to twenty-four hours the erythroblasts assume an appearance intermediate between that of megaloblasts and

normoblasts. Typical normoblasts can already be seen in small numbers. Almost the only megaloblasts still recognizable at this time are late, oxyphilic cells, and these disappear at the end of thirty-six hours. Two days after treatment has begun the transformation is virtually complete and the marrow is normoblastic."

The change in the cellular characteristics is accompanied by an increase of basophilic and, slightly later, of polychromatic cells and by the appearance of numerous mitotic figures. Gradually the distribution of erythroid cells approaches the normal.

According to these authors there is definite evidence that, in the absence of sufficient hemopoietic principle, erythroblasts undergo progressive aberration in structure, as well as function, and that the process is reversible except in cells permanently incapable of mitosis. The lack of hemopoietic principle leads to a disturbance in mitosis, which unless too long continued, responds to specific therapy by a prompt return to normal. In the experience of Zuelzer and his co-workers, folic acid brings about such a return to the normoblastic type of erythropoiesis.

This experience concerning the effectiveness of folic acid in the treatment of megaloblastic anemia of infants and young children is shared by Siebenthal,⁵ who reports two cases in children aged 6 and 17 months, respectively. Siebenthal concludes that "Megaloblastic anemia is a relatively common disease of white infants, and, since a complete and permanent recovery can be effected by folic acid therapy, the condition should be understood by all those caring for small children."

In an article entitled, "Further Observations on the Specificity of the Folic Acid Molecule," Spies and his associates⁶ gave a detailed account of investigations concerned primarily with the mechanism of action of folic acid. These workers undertook a comparative study of the hemopoietic properties of six compounds somewhat related to folic acid in their chemical structure, as shown in persons with Addisonian pernicious anemia, nutritional macrocytic anemia, and tropical sprue in relapse. Of these compounds, only the magnesium salt of formyl pteroyl glutamic acid was effective in producing reticulocytosis and an increase in red blood cells, hemoglobin, white blood cells, and platelets, and this compound was not so effective per unit of weight as folic acid itself. These observations by Spies and his co-workers emphasize the great specificity of the folic acid molecule.

The availability for study of folic acid, a chemically pure substance with remarkably beneficial effects on patients suffering from megaloblastic anemia, offers hope for a more complete understanding of hemopoiesis. Although megaloblastic anemia has been considered of rather rare occurrence in infants and children, it appears that more such cases of anemia occur in this age group than were recognized previously.

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News and Notes

Dr. Julius B. Richmond, of the University of Illinois College of Medicine, is one of the sixteen young scientists appointed as the first group of Scholars in Medical Science, under the plan announced last fall by the John and Mary E. Markle Foundation to support qualified young scientists who wish to make a career in academic medicine. Dr. Richmond's field of research is pediatrics. The grant is made to the University of Illinois College of Medicine, Chicago.

The Foundation has allocated a total of \$400,000 to accredited medical schools, each school to receive \$25,000 payable at the rate of \$5,000 annually for five years. As faulty members of the participating medical schools, the Scholars will devote the next five years to teaching and research, at the end of which time they will have had an opportunity to become established teachers and investigators.

A postgraduate refresher course in general pediatrics will be given the week of May 24 through May 29 by the staff of the Department of Pediatrics of the Washington University School of Medicine. The fee is \$25.00. A detailed circular may be obtained from the registrar of the school, 4580 Scott Avenue, St. Louis 10, Mo.

On February 2, Dr. Lawrence E. Goldman, a member of the staff of the Children's Hospital and the Washington University School of Medicine, Department of Pediatrics, died at the age of 44.

An International Congress on Mental Health will be held in London, England, Aug. 11 through Aug. 21, 1948. There will be three International Conferences, one of which on "Child Psychiatry," with the theme of personality development in its individual and social aspects with reference to aggression, will run from August 11 to August 14. An executive committee of the International Committee for Mental Hygiene, 1790 Broadway, New York, is coordinating preparatory activities in the United States. Inquiries as to further information, application forms, and travel arrangements should be sent to the Executive Office of the Committee, Dr. Nina Ridenour.

The National Foundation for Infantile Paralysis announces the First International Poliomyelitis Conference, to be held at the Waldorf-Astoria Hotel in New York, July 12 through July 17. The American Pediatric Society and the Academy of Pediatrics are among the scientific societies sponsoring the conference. Dr. Hart E. Van Riper is the general chairman. There will be ten plenary sessions. The subjects and presiding officers of the sessions are as follows:

1. "The Importance of Poliomyelitis as a World Problem," Oswaldo P. Campos, M.D., Presiding Officer, Clinical Orthopedic Surgeon, Hospital Jesus, Rio de Janeiro, Brazil.
2. "Poliomyelitis: The Early Stage," Rustin McIntosh, M.D., Presiding Officer, Professor of Pediatrics, Columbia University, New York City.
3. "The Management of Poliomyelitis: The Early Stage," Robert Kno-Song Lim, Ph.D., Presiding Officer, Surgeon General, National Defense Medical Center, Shanghai, China.
4. "Poliomyelitis: The Convalescent Stage," Arthur Steindler, M.D., Presiding Officer, Professor of Orthopedic Surgery, State University of Iowa, Iowa City, Iowa.

5 "The Management of Poliomyelitis—The Convalescent Stage," Arvid Wallgren, M D, Presiding Officer, Professor of Pediatrics, Royal Caroline Medical Institute, Stockholm, Sweden.

6 "The Management of Poliomyelitis—The Late Stage," Carlos S Ottolenghi, M D, Presiding Officer, Docente Libre de Ortopedia, Buenos Aires, Argentina

7. "Bulbar Poliomyelitis," James E. Paullin, M D, Presiding Officer, Professor of Clinical Medicine, Emory University, Atlanta, Georgia

8 "Immunology and Chemotherapy in Poliomyelitis," Pierre L LePine, M D, Presiding Officer, Director of Laboratories, Pasteur Institute, Paris, France

9 "The Public Health Aspects of Epidemic Poliomyelitis," Harry S Mustard, M D, Presiding Officer, Commissioner of Health, New York City.

10 "Poliomyelitis Throughout the World," Thomas Parran, M D, Presiding Officer, Surgeon General, United States Public Health Service, Washington, D C. Official delegates will be asked to present reports on poliomyelitis problems in their countries

Details as to accommodation, etc, may be obtained from the Conference Committee, Room 571, Waldorf Astoria Hotel, New York 22, N Y.

Book Reviews

Sexual Behavior in the Human Male. A C Kinsey, W B Pomeroy, and C E Martin, Philadelphia, 1948, W. B Saunders Co, 804 pages Price \$6 00

Some ten years ago Dr Kinsey, professor of zoology at Indiana University, became interested in human sexual behavior as the result of his inability to find educational material based on facts rather than on opinion and preconceived ideas of what sexual behavior should be. This interest gradually developed into a remarkable study, which in recent years has been financed by the Rockefeller Foundation. Some 12,000 detailed histories of sex life have been obtained in personal interviews by Dr Kinsey and his associates, a number which they plan to expand to 100,000. This report is the first of a series of eight planned volumes analyzing the material, and is based on the data obtained from 5,300 white males. The first consideration is the validity of the data and their statistical analysis. This is gone into in detail in the first four chapters, and one can conclude only that the data presented are valid. While data based on many more thousands would undoubtedly lead to some differences in the figures, we doubt very much if the changes would be of any importance.

The material is presented in an objective way, and the authors make no attempt to draw conclusions other than those shown by the data, nor to go into the moral and social implications of their findings. It is a difficult book to review without quoting innumerable detailed statistics, and analyzing the statistics is a thing best left to the reader.

The data show that there are enormous variations in the individual pattern of sexual behavior, and that it is practically impossible to define a norm. One of the striking differences in the pattern is found when the data are analyzed according to educational levels. Rural and urban groups likewise show marked differences. Some of the data are quite startling to our preconceived ideas, as, for example, the peak of sexual activity occurring in adolescence and the early twenties. On the other hand, that some 88 per cent of single men in adolescence and early maturity practice masturbation is not startling news to the physician. The data show that some 70 per cent of preadolescent boys have had sex play between the first year and puberty. Another interesting finding is the relatively small part that prostitution plays in the sexual life of the white male. Despite the care with which the data on homosexuality have been presented, we fear they will be misinterpreted. The frequency with which some homosexual experience has taken place at some time in an individual's life does not mean that roughly one in four men is homosexual. The authors state this clearly.

It is a study of tremendous importance, not only to the physician but equally to the educator and sociologist. It cannot help but have an influence on our laws and penology. The findings will undoubtedly be very upsetting to many, particularly those who look upon sexual behavior as a matter coming under the domain of the moral and religious fields. To the physician and scientist, the important thing is that for the first time the facts of sexual behavior are presented. These facts should lead to a much greater tolerance to what in the past as a result of moral teaching has been looked upon as abnormal.

B. S. V.

The Rh Factor in the Clinic and the Laboratory. Edited by Joseph M. Hill, M.D., and William Dameshek, M.D., New York, 1948, Grune and Stratton, pp. 192.

This volume, a special issue of *Blood, The Journal of Hematology*, consists of a series of papers read at the Dallas-Mexico City Congress in November, 1946. Dr. Philip Levine in "A Survey of the Significance of the Rh Factor" reviews the general Rh problem, and R. R. Race presents an excellent résumé of "The Rh Genotypes and Fischer's Theory," describing the CDE or Fischer-Race nomenclature, which is now rapidly supplanting that of Wiener. Among the nine other papers included in the volume, those on "Hemolytic Mechanisms" by William Dameshek and "The Treatment of Erythroblastosis Fetalis by Substitution Transfusion" by Harry Wallerstein are of special interest.

J. V. C.

Pediatría. XVI Curso de Perfeccionamiento 1945. From the Institute of Clinical Pediatrics and Infant Hygiene "Dr. Luis Morquio," Montevideo, Uruguay, 1947, Impresora L. I. G. U., pp. 710.

A collection of papers by the staff of the Morquio Institute, of which Dr. José Bonaba is director. The first section on the infectious diseases contains, among nine contributions, a discussion of B.C.G. vaccination by Dr. Abelardo Saenz. The second section is concerned with the infant, and the third with surgery. A fourth section on "diverse themes," contains an interesting article by Dr. Piaggio Garzon on "puericulture in art" with some fifty-odd illustrations tracing the subject down through the centuries, and one on the muscles in Heine-Medin's disease by Prof. Dr. Victor Escardo Y. Anaya. The scope of the subjects considered in the volume speaks highly for the many-sided interests and scope of the work of the Morquio Institute.

The Foot and Ankle: Their Injuries, Diseases, Deformities, and Disabilities. Philip Lewin, M.D., ed. 3, Philadelphia, 1947, Lea & Febiger, pp. 847. Price \$11.00.

The latest edition of this most complete treatise has been uniformly enlarged over the second edition principally by including in the appropriate chapters many observations and conclusions of the military and naval experience during World War II. While worth-while information has been added to the text, the 102 new illustrations are probably the most valuable addition to the book.

Practically every disease, injury, new growth, and deformity of the foot and ankle in all age groups is discussed to some degree; and, while the broad coverage prevents an exhaustive presentation of each subject, the majority are presented in sufficient detail to afford the reader adequate working information. It should be a valuable reference book for the pediatrician and internist because it will afford physicians of these specialties a ready consultation on the surgical approach to many problems of the foot and ankle with which they are confronted. It also merits a place on the library shelves of every general surgeon, orthopedic surgeon, and general practitioner.

O. P. H.

Editor's Column

"SEXUAL BEHAVIOR IN THE HUMAN MALE"

OCCASIONALLY a scientific work which is essentially medical in nature has influence and repercussions far beyond the field of medicine. Such we believe will be the case with Kinsey's study of the *Sexual Behavior in the Human Male*, which is reviewed elsewhere in this issue. It throws much light and information on a subject which for centuries has been clouded with taboos, customs, and moral and religious teachings. It will be the cause of tremendous controversy and discussion, and undoubtedly even more as the succeeding volumes of the study of sex behavior appear. Physicians will hold to the view that the presentation of scientific facts is the essential thing, and that the upsetting of conceptions based on what people think should be the facts is of secondary importance. Medical thought will be influenced chiefly in the field of psychiatry. On the other hand, the study will have a decided impact on the social, educational, and juridical fields of thought. It is a book that must be slowly and carefully read and one that is difficult to discuss adequately in a review. The more one studies it, the greater becomes the respect for the sincerity and integrity of Professor Kinsey and his associates. Every physician sooner or later must become familiar with the study.

Some criticism has already been expressed that its circulation has extended so early beyond the medical profession. According to a newspaper report, over 200,000 copies have been printed and distributed within a few weeks after publication of the book. We cannot agree with this criticism, for as has been stated, it is a scientific study whose importance extends far beyond the field of medicine.

THE BRITISH MEDICAL ASSOCIATION PLEBISCITE

The February issue contained an account of the medical controversy in Great Britain, which told of the vote to be taken by the B. M. A. on January 31.

According to press dispatches, British physicians voted overwhelmingly against the medical service plan proposed by the British Labor Government, which is now in power. Eighty-two per cent of the 56,000 members of the association voted, with 89.6 per cent of those voting opposed to the proposed plan. The total vote was 40,816 opposed to 4,735 in favor. A further question as to whether they would accept service under the plan, provided the majority voted against it, was asked of the practitioners and specialists who would furnish the personnel to carry out the plan. The vote was 24,066 (86 per cent) against accepting service and 4,495 in favor. This leaves but 3,560 general practitioners and 971 consultants and specialists to operate the plan for a population of 47,000,000 if the 24,000 who voted against accepting service boycott the act, which is voluntary and not compulsory for the physician.

The B. M. A. was severely and vehemently criticized in the Commons by Minister of Health Bevan, and by a majority vote along party lines the act was sustained in face of the opposition of the British physicians to its present provisions. The government has stated that despite the medical opposition the act will be put into effect on July 5.



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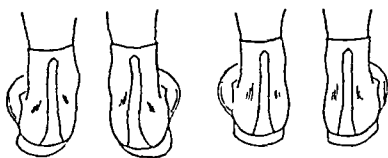
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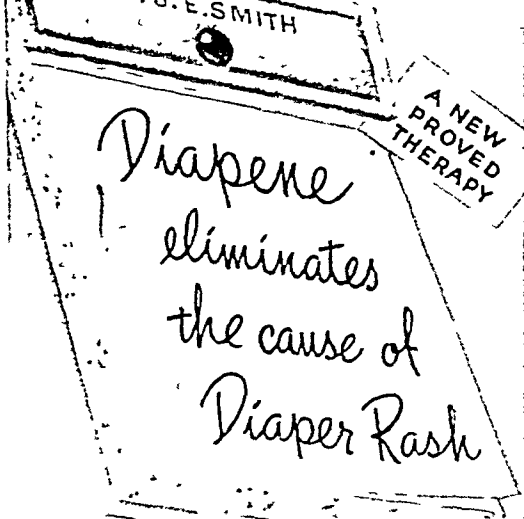


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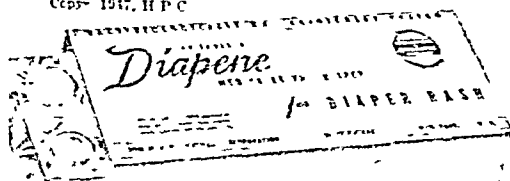
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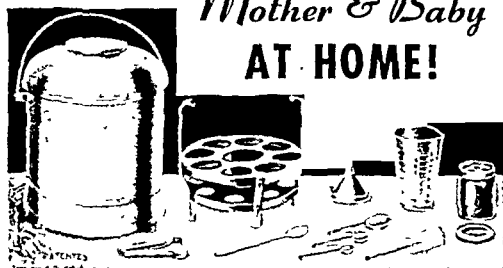
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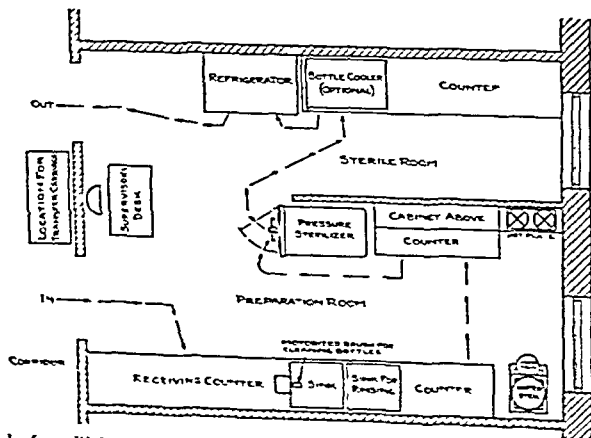
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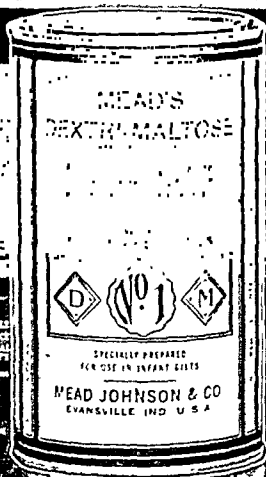
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infant feeding that consistently, for over three decades, has received universal pediatric



recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Dextrin-Maltose.

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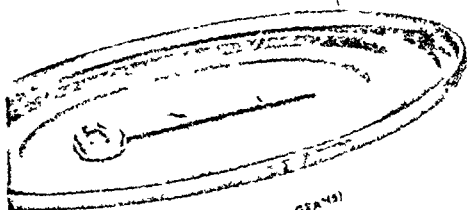
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References: 1 Dodd, K. and Minor, A. S. *J. Pediat.*, 8: 442, 1936.
2 Dodd, K. and Minor, A. S. *J. Pediat.*, 8: 452, 1936.
3 Sahyun, M. *Am. J. Dig. Dis.*, 13: 59, 1946.

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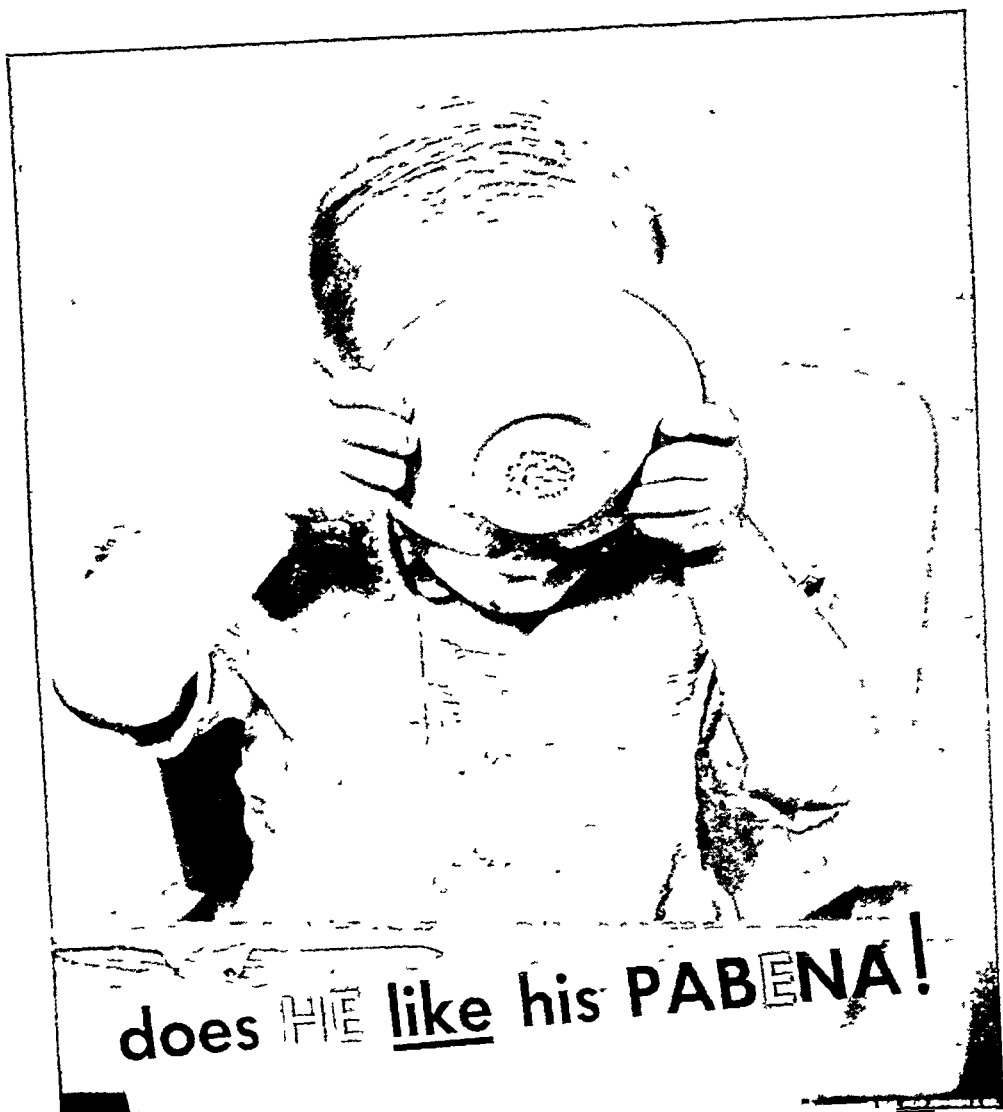
For adults, use the same dosage as that recommended for oil-wax preparations. For infants, 0.2 cc. (60,000 units); children up to ten years, 0.5 cc. (150,000 units); and children over ten years, 1 cc. (300,000 units).

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by

P. C. Jeans, A.B., M.D. and Williams McKim Marriott, B.S., M.D.

The C. V. Mosby Company

Fourth Edition 1917

- "The neuromuscular maturity of the mouth and throat is sufficiently developed by the fourth month so that the infant can be taught to take semisolid food from a spoon. Some infants can learn this procedure earlier . . ." Page 37
- "When teaching a baby to take a new food or one he dislikes, he should be given at first only a small amount, with gradual increase to a normal serving. Likes and dislikes of food are the result of habit, and habits are acquired relatively easily in infancy." Page 249
- "Vegetables should have an important place in the diet after the first few months of infancy." Page 243
- "Protein digestion and absorption during infancy are remarkably complete . . ." Page 138
- "Several of the prepared baby soups sold contain finely divided meat. Some of these are known as vegetable soups with cereal and meat . . ." Page 245



How Campbell's Baby Soups Contribute to Infant Diets

They do it by combining many needed food elements in each of the five kinds!

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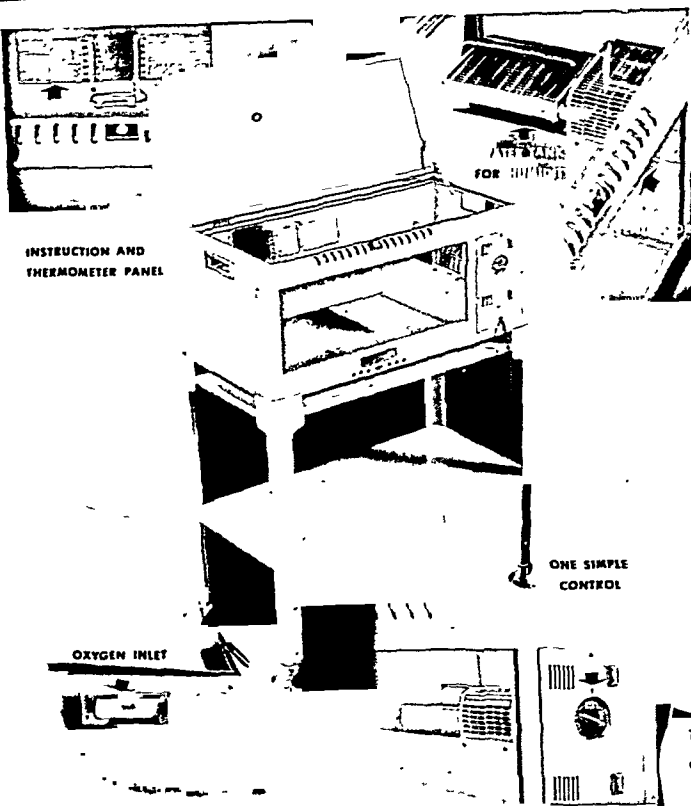
The fifth, the Vegetable Soup, combines 8 vegetables and oatmeal. It can serve as vegetables for an egg yolk-and-milk feeding.

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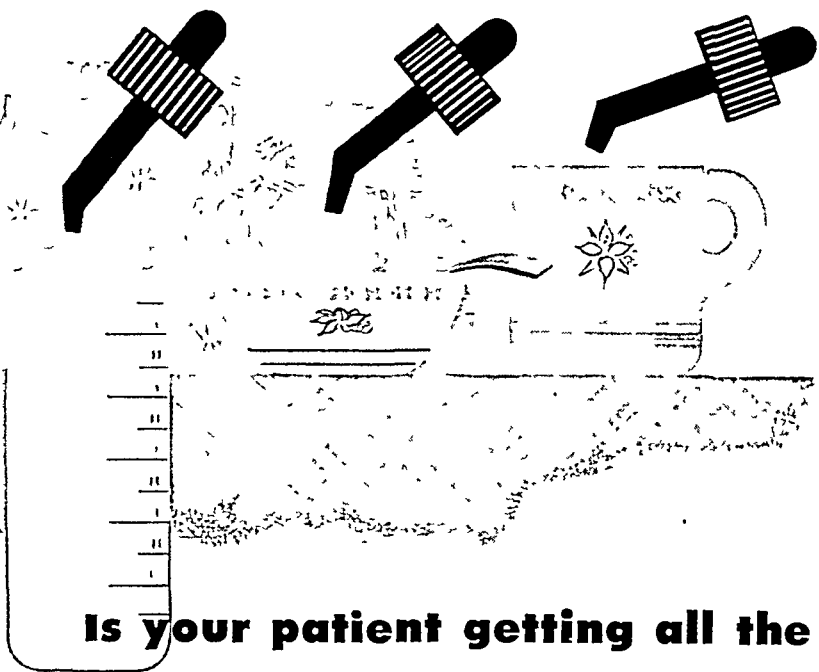
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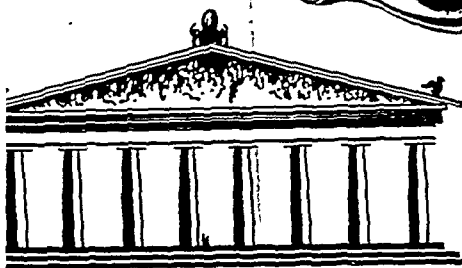
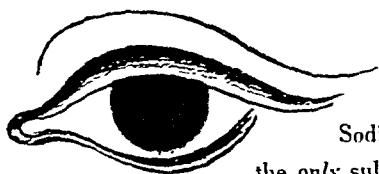
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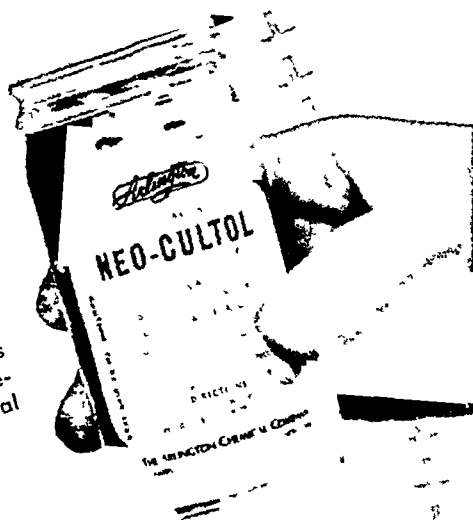
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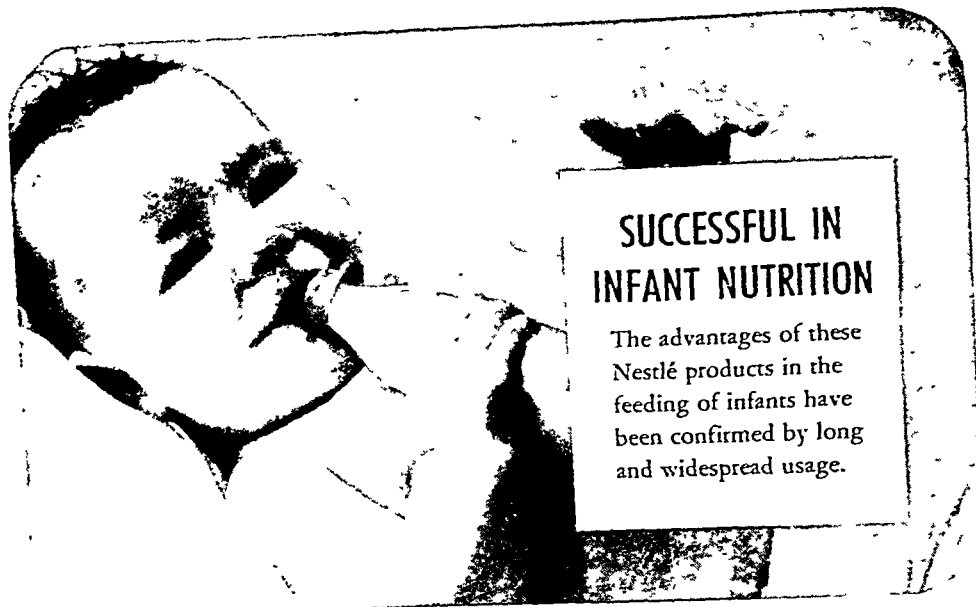
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Sulfa-Ceepryn **Cream**

Sulfathiazole, Sulfanilamide and Cetylpyridinium Chloride

rapid absorption of the active ingredients.

Sulfa-Ceepryn Cream is equally effective in other dermatological pyogenic infections, also adjunctively in varicose, wound, and abscess infections, following surgical drainage. Bandaging is not contraindicated. Complete literature and sample on request.

Sulfa-Ceepryn Cream is available at prescription pharmacies in 1-ounce tubes and 1-pound jars

Trademarks "Sulfa-Ceepryn" and "Ceepryn" Reg. U. S. Pat. Off.



THE WM. S. MERRELL COMPANY • CINCINNATI, U. S. A.

*Is it liquid?
Are the crystals
large enough?*

FACTORS TO BE
CONSIDERED
in the use of Penicillin G
in oil and wax

November 1, 1947:
J.A.M.A. 135:567

"On the basis of ease of administration as well as on the concentrations of penicillin achieved in the blood, the liquid preparations of crystalline penicillin of large particle size are recommended as the most satisfactory form of penicillin in oil and wax."

The new Squibb liquid Penicillin G in Oil and Wax

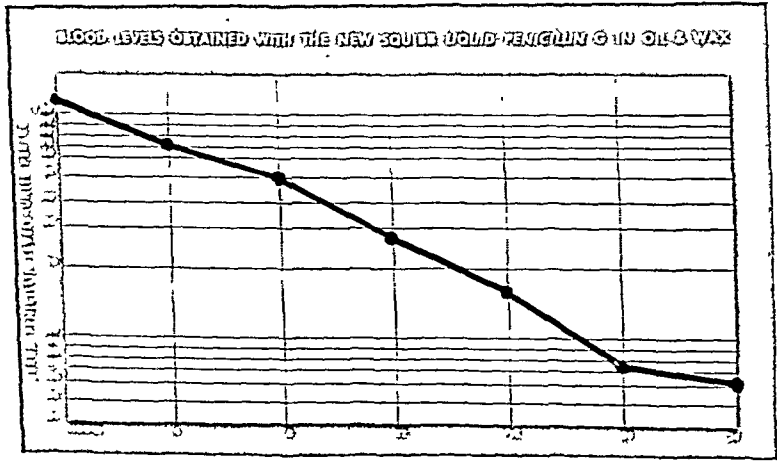
IN 10 CC. VIALS for mass injections in clinic, hospital or office offers these advantages:

OPTIMAL BLOOD LEVELS: achieved with *large particle size crystals*, as found in liquid preparations with "50 per cent or more of the total relative weight of particles measuring greater than 50 microns."

EASE OF ADMINISTRATION: easy to inject without heating.

RESUSPENSION READILY ATTAINED: adequate air space in vial permits shaking to resuspend contents at time of use.

MAXIMUM ACCURACY: properly resuspended, each cc. contains 300,000 units crystalline penicillin G sodium. Even last dose withdrawn easily, accurately.



— showing, even at the end of 24 hours, an average level of 0.062 units per cc. — well above what is usually considered a therapeutic level.

Optimal size crystals are also present in Double-Cell Cartridges of Squibb Penicillin G in Oil and Wax. For individual injection

at home or office. Cartridges contain 300,000 units, full single dose. In B-D* disposable or permanent syringe.

SQUIBB MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

March, 1948

*TRADEMARK REG. SECTION, DICKINSON & CO



WHEN AN

Ounce of Prevention

CAN MEAN SO MUCH

In children, food resistance which reduces nutrient intake to below required amounts, can exert a far-reaching influence on physical and mental development. Through the simple expedient of including in the daily dietary three glassfuls of the food drink made by mixing Ovaltine with milk, such nutritional deficiencies are readily prevented.

This dietary supplement, enjoyed by all children, provides generous

amounts of all nutrients considered essential: high quality protein, B complex and other vitamins including ascorbic acid, readily utilized carbohydrate, easily emulsified fat, and the important minerals calcium, phosphorus, copper, and iron. A special favorite with children, Chocolate Flavored Ovaltine is again in full supply; its nutritional composition is virtually identical with that of plain Ovaltine.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	659	VITAMIN A	3000 I U
PROTEIN	32.1 Gm.	VITAMIN B ₁	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	2.00 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.



GIVING MILK THE GREEN LIGHT!

W

WHEN MILK IS A VITAL PART of the daily regimen, such as in infancy, childhood, pregnancy, and for gastro-intestinal, postoperative and geriatric conditions—a serious aggravation of the dietary problem may occur for those patients who (either for physiologic or psychologic reasons) are unable to ingest this essential nutrient.

In such cases, the *red light* of milk refusal may be quickly changed to the *green light* of eager acceptance—by transforming the liquid milk into deliciously flavored, tasty rennet desserts, through the medium of rennet powder or household rennet tablets.

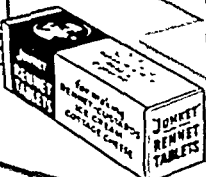
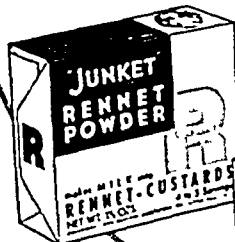
Young and old alike relish these temptingly smooth custard-like desserts which incorporate the uncooked milk—with all nutritional factors unchanged—into a variety of delicious, colorful rennet desserts. They're so simple to prepare—and are more easily digested than milk itself, because of the softer, more friable curds formed in the stomach.

"JUNKET" RENNET POWDER—already sweetened—comes in six popular flavors;

"JUNKET" RENNET TABLETS are not sweetened or flavored—just add sugar and flavor to taste.

Delicious, highly acceptable rennet desserts may be made with either.

"JUNKET" is the trade mark of Chr. Hansen's Laboratory, Inc., for its rennet and other food products, and is registered in the United States and Canada.



"JUNKET" BRAND FOODS

Division of Chr. Hansen's Laboratory, Inc.
LITTLE FALLS, N. Y.

B-3S

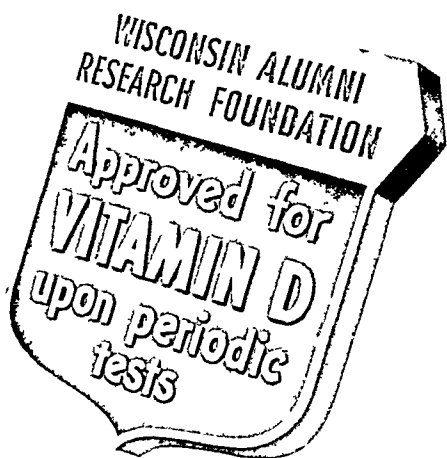
In 1544 the lion passant was adopted as the official silver stamp by the Goldsmiths Hall in London. After years of disuse, the mark reappeared again in 1719. Even today London silver carries this hallmark—a symbol of excellence and quality.



MARKS OF

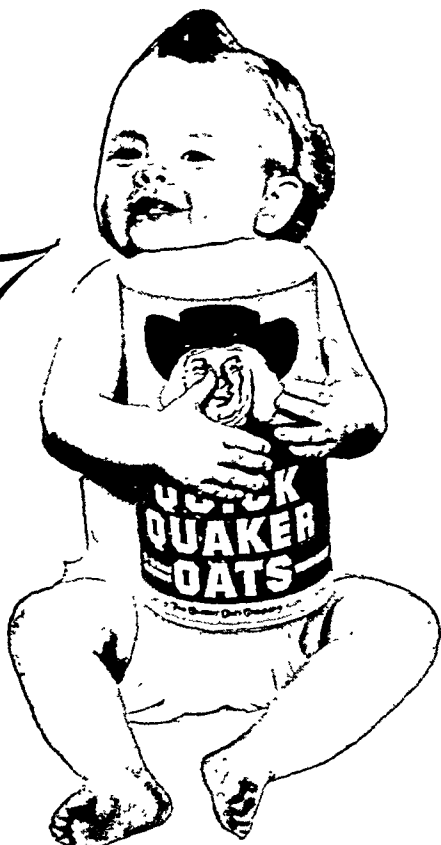
Quality

In 1948 the seal of the Wisconsin Alumni Research Foundation is recognized as a symbol of quality, because it attests to the Vitamin D content of the product which bears it. It guarantees that the product is subjected to the Foundation laboratory tests regularly and is found to meet the high standards of quality required. For over 20 years the medical profession has advised its patients to "look for the Foundation Seal" with full confidence of quality.



WISCONSIN ALUMNI *Research* FOUNDATION
MADISON 6, WISCONSIN

*Here's the
Cereal
for Me!*



**To supplement
baby's milk diet**

... Whole-grain Oatmeal is Richest Natural Cereal in Protein, Vitamin B₁, Food-Energy and Iron

In selecting a cereal supplement for the infant's diet, the pediatrician's first interest is the nutritional value. With regard to parents, economy also deserves consideration. A happy solution is offered in Quaker Oats. As a rich, thrifty source of Protein, Vitamin B₁, Food-Energy and Iron, whole-grain oatmeal leads all natural cereals.

A complete discussion of the nutritional value of oatmeal in the diet of infants and children is given in this new booklet prepared for use of the medical profession:

... Honey was used for these tests because it is 1, of guaranteed full strength and uniformity. Under controlled conditions to regulate flavor

... send you a small supply of Lake Shore Honey may observe results in your own practice.

... e of Honey as a Carbohydrate in Infant Feeding," by Schlutz, M.D., and Elizabeth M. Knott, Ph.D., Journal of Pediatrics, Vol. 13, No. 4, 465-473, October 1938

... ect of Honey Upon Calcium Retentions in Infants," by Knott, Ph.D., C. F. Shukers, M.D., and F. W. Schlutz, Journal of Pediatrics, Vol. 19, No. 4, 485-494, October 1941. "Morrhagic Vitamin Effect of Honey," by A. E. Vivino, Jaydak, L. S. Palmer and M. C. Tanquary, Proceedings Society for Experimental Biology and Medicine, 1943, 53, 9-11.

Quaker Oats



**The World's
Best-Tasting
Breakfast Food**

*Quaker and
Mother's Oats
Are the Same*



W. F. STRAUB & COMPANY
5510 Northwest Highway, Chicago 30, Ill.
Please send me a small supply of LAKE SHORE
HONEY for use in my practice.
(Please write your name and address
in the margin.)

**"Just as regularly as orange juice and
also prescribe a substance rich**



Pharmaceutical Manufacturers, Newark 7, N. J.

ice and cod liver oil are prescribed, one should
ice rich in vitamin B for the infant dietary..."

AS long as 20 years ago Hoobler¹ (quoted above) advocated routine supplementation of the infant dietary with a good source of vitamin B factors. He, as well as other investigators, recognized that symptoms of partial vitamin B deficiency observed in infants are often traceable to the fact that both human and cow's milk are relatively lacking in certain B factors.

Five drops daily of White's Multi-Beta Liquid provides a generous supply of all clinically important B vitamins *in proportion to their inadequacy* in the average infant diet and offers, in addition, a simple means of managing the commonly encountered gastro-intestinal disturbances of infancy.

Pleasant tasting, it is easy to take in milk mixtures, orange juice, soft feedings or directly from the dropper.

1. Hoobler, B.R.: Symptomatology of Vitamin B Deficiency in Infants, J.A.M.A., 91:307-310 (Aug. 4) 1928.

5
M

Liquid

47, 111

Economic Sense

APPRAISED BY RESEARCH

"Because calories produced from animal fat require more land and labor than those derived from vegetable fat, the latter source is a cheaper one. The relative value in the diet of these sources is an important question both economically and physiologically. At the present time there is no physiologic evidence which justifies any generalization that animal fats are nutritionally superior to vegetable fats."

Excerpt from editorial entitled "An Adequate Diet, I: Calories and Fats"—*Journal of the Medical Society of the State of New York*, January 15, 1945.

CONFIRMED IN DAILY LIVING



The Miller children—
(Front row) Wayne, Twila, Karen Regina.
(Back row) Dolores, Gloria, Dewain.

Mrs. Lloyd Miller, whose six children greet you from the photograph at left, has served Nucoa at her table for thirteen years. "I use six to eight pounds a week," she says. "Nucoa always tastes sweet and fresh and it's so reasonable in cost I needn't be stingy with it. Growing children and men who work hard need plenty of nourishing spread for their bread."

Nutritionists agree with Mrs. Miller. And the Miller children, like millions of others brought up on a "bread 'n' Nucoa" economy, confirm the conclusion of science as to the physiological adequacy of a vegetable fat. Test Nucoa in your own home. Its uniform deliciousness will give you confidence, we believe, in recommending Nucoa for nutritional value at moderate cost.

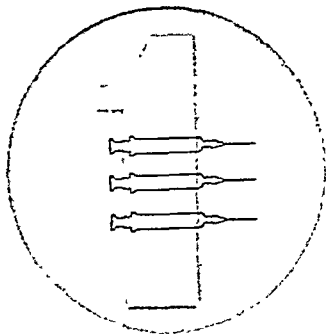
The chief ingredients of Nucoa, America's foremost margarine, are pure vegetable oils churned with fresh pasteurized skim milk. The first margarine to add Vitamin A, Nucoa was also first to insure today's high fortification of 15,000 U.S.P. units in every pound.



©1945 NUCOA. REG. U. S. PAT. OFF.

Nutritious NUCOA

WITH 15,000 U.S.P. UNITS OF VITAMIN A



*comprehensive
protection
with a*
**SINGLE
INJECTION**

The use of Diphtheria and Tetanus Toxoids, Alum Precipitated, and Pertussis Vaccine Combined, has largely replaced the practice of repeated injections for immunization against specific infections. These combined antigens produce an immune titer equal to or greater than that effected by the antigen injected individually. The *simultaneous triple defense* provided by this comprehensive treatment greatly reduces the incidence of contagion in a community and makes possible a reduction of infant mortality rate.

Recommended for infants and pre-school age children, immunization consists of three 0.5 cc. subcutaneous injections at intervals of from four to six weeks.

Antigenic content of *H. pertussis* increased to 45,000 million organisms per immunizing treatment.

SUPPLIED :

Single Immunization package contains three $\frac{1}{2}$ cc. Vials
Five Immunizations package contains three $2\frac{1}{2}$ cc. Vials.



THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.



PHARMACEUTICALS, BIOLOGICALS, BIOCHEMICALS FOR THE MEDICAL PROFESSION

**DIPHTHERIA and TETANUS TOXOIDS,
ALUM PRECIPITATED,
and PERTUSSIS VACCINE COMBINED**



The New Oral Method of Penicillin Administration to Infants and Children



Soluble Tablets Crystalline Penicillin provide a new and convenient means of instituting penicillin therapy in infants and young children. These small tablets of crystalline penicillin G potassium are composed entirely of penicillin, and contain neither binder nor excipient. Readily soluble, they may be administered with the milk formula to infants, or dissolved in milk or water before being given to young children. Thus the need for hypodermic injection is obviated in the treatment of many penicillin-responsive infections and administration can be made by the mother. Their presence in solution produces no discernible alteration in taste. Dosage, 100,000 units or more every 3 to 4 hours.

Each Soluble Tablet Crystalline Penicillin contains 50,000 units and is individually sealed in aluminum foil.

Supplied in boxes of 24 tablets and available at all pharmacies.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION
17 E. 42nd ST., NEW YORK 17, N. Y.

Soluble Tablets
Crystalline Penicillin



Formulac

**a complete
infant food**



FORMULAC Infant Food is a concentrated milk, in convenient liquid form, containing *all the vitamins and minerals* a normal infant is known to need. Inclusion of the vitamins *in the milk itself* lessens the risk of error in supplementary administration.

No carbohydrate has been added to FORMULAC. This permits you to prescribe both the type and the amount of carbohydrate best suited to the child's individual needs. Addition of the carbohydrate and water creates a complete infant food.

FORMULAC is promoted ethically. It has been clinically tested and proved an excellent basis for both normal and difficult feeding cases, retaining its vitamin-potency on storage.

A product of National Dairy research, FORMULAC is available at drug and grocery stores throughout the country. It is economically priced.

DISTRIBUTED BY KRAFT FOODS COMPANY

NATIONAL DAIRY PRODUCTS COMPANY, INC.
NEW YORK, N. Y.

For further information about FORMULAC, drop a card to National Dairy Products Co., Inc., 230 Park Avenue, New York 17, N. Y.



NOW... a New, Effective ANTI-HISTAMINIC of Low Toxicity

Clinical studies have established Neo-Antergan Maleate (brand of pyranisamine maleate) as an efficient antihistaminic drug of relatively low toxicity, effective in preventing or relieving symptoms in a high percentage of patients with certain allergic manifestations.

Neo-Antergan has proved to be most effective in the following conditions:

URTICARIA • HAY FEVER • ALLERGIC
DRUG REACTIONS • VASOMOTOR RHINITIS
PRURITUS • ATOPIC DERMATITIS AND
ANGIONEUROTIC EDEMA.

Beneficial results are obtained also in
bronchial asthma and eczema, but in a
lower percentage of cases. Certain cases

of migraine, presumably those due to
histamine or a histaminelike substance,
and some cases of abdominal pain
thought to be caused by smooth muscle
spasm induced by allergic phenomena,
also may be expected to respond in
varying degree to treatment with Neo-
Antergan. The action of Neo-Antergan
is palliative, not curative.

Undesirable reactions are generally
mild and transient, although moderately
severe side effects have been observed
in a relatively small percentage of cases.
It is rarely necessary to discontinue
treatment with Neo-Antergan because
of toxic reactions.

NEO-ANTERGAN[®] MALEATE

(Brand of Pyranisamine Maleate)

(N-2-methoxybenzyl-N',N'-di-
methyl-N-2-pyridylethylam-
ine maleate)



MERCK & CO., Inc.
Manufacturing Division
RAHWAY, N. J.





Premature, but promising

To the premature struggling for existence, intestinal distention, colic or diarrhea may be insurmountable obstacles. Good care and good nutrition, however, offer promising prospects for life and health.

In the feeding of premature infants, 'Dexin' has proved an excellent "first carbohydrate." Because of its high dextrin content, it (1) resists fermentation by the usual intestinal organisms, (2) tends to hold gas formation, distention and diarrhea to a minimum, and (3) promotes the formation of soft, flocculent, easily digested curds.

Readily soluble in hot or cold milk, or other bland fluids, 'Dexin' brand High Dextrin Carbohydrate is well taken and retained. 'Dexin' *does* make a difference.

'Dexin'

HIGH DEXTRIN CARBOHYDRATE
BRAND

Composition—Dextrins 75% • Maltose 24% • Mineral Ash 0.25% • Moisture 0.75% • Available carbohydrate 99% • 115 calories per ounce • 6 level packed tablespoonfuls equal 1 ounce • Contains of twelve ounces and three pounds • Accepted by the Council on Foods and Nutrition, American Medical Association

'Dexin' Reg. Trademark

Literature on request



BURROUGHS WELLCOME & CO. (U S A) INC., 9 & 11 East 41st St., New York 17, N. Y.

March, 1948

Page 27

widening the range

of spasmolytic therapy with
the new, unique

DONNATAL elixir

Donnatal—outstanding spasmolytic and
sedative—is now available in liquid form!

Donnatal Elixir fills a long-felt need,
particularly among pediatricians, for
the treatment of pyloric stenosis, intestinal
colic, diarrhea and enuresis. For adults
too, patient preference may suggest
the Elixir in place of the Tablets—each 5 cc.
(1 teaspoonful) providing the therapeutic
effect of 1 tablet.

Important new evidence on Donnatal
attests its unusual clinical efficacy
and its advantages over single
drugs and synthetics.

A. H. ROBINS COMPANY

RICHMOND 19, VIRGINIA

Ethical Pharmaceuticals of Merit since 1878

formula Each teaspoonful (5 cc.) contains:
Hyoscyamine Sulfate0.1037 mg.
Atropine Sulfate0.0194 mg.
Hyoscine Hydrobromide 0.0065 mg.
Phenobarbital (1/4 gr.)..... .16.2 mg.



DONNATAL

Another Robins' Triumph

elixir

A NEW RALSTON SERVICE

Designed To Help You!

Free! FEEDING DIRECTION FORMS
FOR YOUR YOUNG PATIENTS

Four Forms For Four Age Groups

- birth to 3 months
- 3 to 6 months
- 6 to 10 months
- over 10 months

Easy To Use—Complete—Adaptable

Each form contains:

Weight record to be kept between office visits.

Formula and diet charts for you to fill out.

Adjustable feeding time-schedules for each age group.

Lists of foods which you may add to or delete from.

Food preparation suggestions.

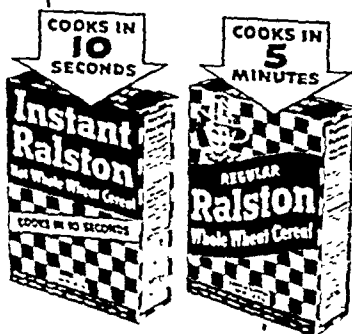
Spaces for prescribing sun baths or writing other directions.

☆ ☆ ☆

Available in pads of 50 each, imprinted with your name and address, if you wish.

WHEN YOU RECOMMEND CEREAL . . .

Remember — Hot Ralston is whole grain wheat with extra wheat germ—2½ times as rich in wheat germ as whole wheat itself. May we suggest you keep Hot Ralston in mind for your patients?



MAIL THIS COUPON TODAY!

Ralston Purina Company, Nutrition Service
JP-6 Checkerboard Square, St. Louis 2, Mo.
Please send, no cost or obligation, samples of Feeding Direction forms, C848, so I may order pads as needed.

Name.....
Address.....
City.....
Zone..... State.....

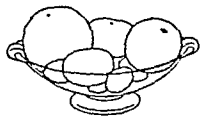
OFF TO A FLYING STAR

*with greater nutritional
impetus from citrus fruits!*

"After birth, the rate of growth and development of the infant depends in large measure on the adequacy of his nutrition."⁴ And of vital concern is vitamin C. Its developmental effect on collagenous formation²—with marked strengthening of intercellular substance and protection of tissue integrity⁹—plus attendant increases in growth and stamina³, bodily vigor⁰ and resistance to disease⁸, strikingly indicate ascorbic acid's role during this critical period.

Uniquely qualified to meet this need are the citrus fruits and juices, fresh or canned. Their universal appeal and nutritional value as rich natural sources of vitamin C and other essential nutrients* are almost without parallel among foods. Their tart goodness in stimulating appetite¹. . . their active aid to digestion⁶ (with added protection against gastric bacterial invasion⁷). . . improved calcium utilization¹ and mild laxation⁸. . . and their ready source of quick energy⁵ for active growing bodies . . . these all make their inclusion in the pediatric dietary regimen highly desirable.

FLORIDA CITRUS COMMISSION • LAKELAND, FLORIDA





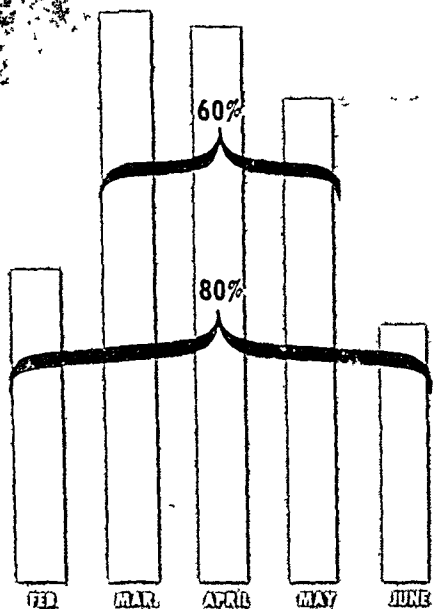
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2. Dalldorf, G.: In the Vitamins, American Medical Association, Chicago, 1939.
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6. Manchester, T.C.: Food Research, 7:394, 1942.
7. Mattice, M.R.: In Dietetics for the Clinician, M. A. Bridges, Lea & Febiger, Philadelphia, 1941.
8. Rose, M.S.: Rose's Foundation of Nutrition, Revised by G. MacLeod and C. M. Taylor, Macmillan Co., New York, 4th ed., 1944.
9. Sherman, H.C.: Chemistry of Food and Nutrition, Macmillan Co., New York, 7th ed., 1946.

**Citrus fruits are among the richest known sources of vitamin C; they also contain vitamins A, B₁, G and P, and other nutritional factors such as iron, calcium, citrates, citric acid and readily assimilable fruit sugars.*

FLORIDA

Oranges • Grapefruit • Tangerines • Limes



The above graph of measles incidence based on U S Public Health figures for a ten year period is supported by current reports of present measles incidence

The measles peak is
RIGHT NOW!



**You can prevent or modify measles
without fear of side reactions* with**

IMMUNE SERUM GLOBULIN—CUTTER

Right now, when 60% of all measles occur, is a good time to remember Cutter Immune Serum Globulin, a product of human blood fractionation

In measles serum, it's the gamma globulin that counts. And Immune Serum Globulin—Cutter, contains 160 mgm. gamma globulin per cc. This known and constant potency permits low volume and adjustable dosage.

Second in importance is the blood source—fresh venous whole blood in

the case of Cutter. Immune Serum Globulin contains no placental material.

You can always tell Immune Serum Globulin—Cutter—it's water clear and hemolysis-free. Each 2 cc. vial contains antibodies equal to 40 cc. of original normal serum.

For more information, write Dept. 34, Berkeley 1, California, or ask your Cutter representative.

CUTTER

Fine Biologics and
Pharmaceutical Specialties

**No cases of reaction resulting from use of Cutter Immune Serum Globulin have been reported*

To Forestall

"the emotional pull away from a good diet"



What mother hasn't encountered this emotional pull!
And what mother wouldn't welcome your help in
combating it! Here is help—in CEREVIM.
For this delicious cereal-food appeals to most children
. . . they take it without coaxing.

CEREVIM

a first among first foods

And CEREVIM is so high in vitamins and minerals that even when children rebel against a well-rounded diet, this pre-cooked cereal alone supplies generous amounts of protective factors. A single 1-ounce serving of CEREVIM furnishes the recommended daily allowance of iron, thiamine, riboflavin, and niacin for children up to 3 years of age (as well as 8 times the calcium in a fluid ounce of milk).²

CEREVIM is a truly valuable ally for the physician and the mother when children become "feeding problems."

1. Clair E. Turner (address to the Institute on Social Medicine, Centennial, New York Academy of Medicine).

2. National Research Council, Recommended Dietary Allowances, 1945.

Trade-Mark CEREVIM—Reg. U.S. Pat. Off.



LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY • NEW YORK 20, NEW YORK

The combined clinical value and safety of White's Sulfathiazole Gum has been amply confirmed by longer professional use than any other local chemotherapeutic or antibiotic agent.

HOW EFFECTIVE

HIGH topically effective salivary concentrations of sulfathiazole—averaging 70 mg. per cent—are maintained by chewing a single tablet for one hour.

HOW SAFE

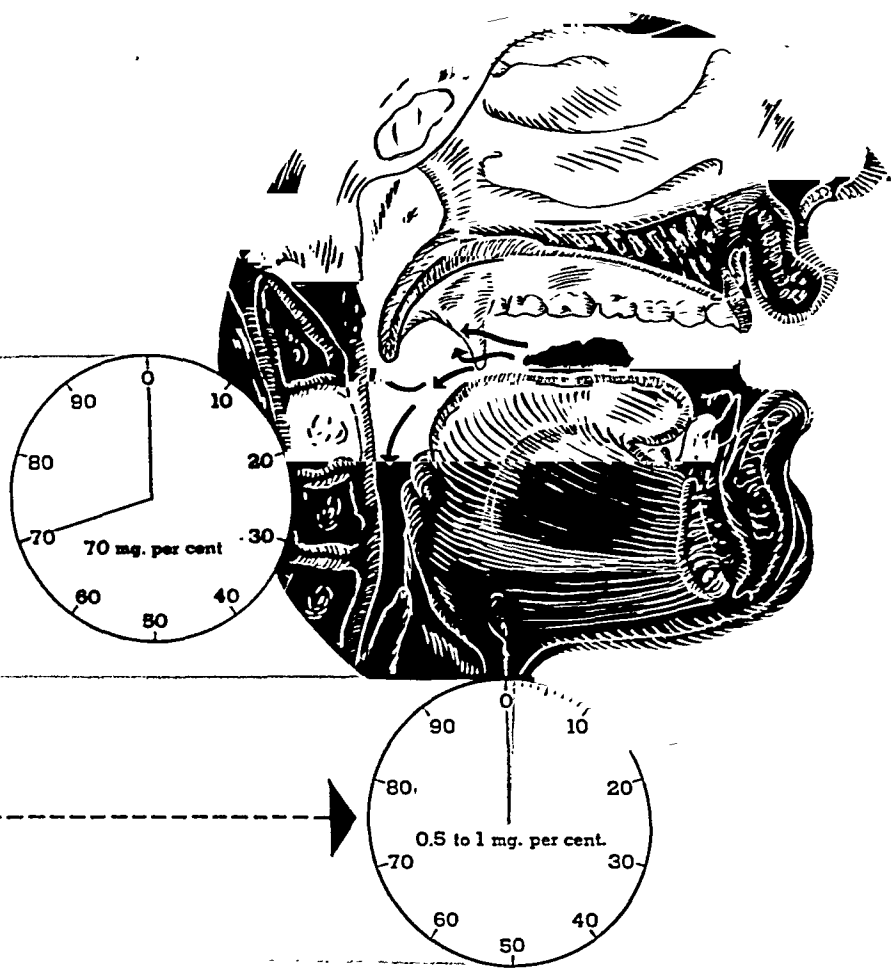
Systemic absorption is practically negligible even with maximal dosage. Blood levels are usually immeasurable—rarely approach 0.5 to 1 mg. per cent under intensive therapy—the possibility of toxic reactions is virtually ruled out.

The topical antibacterial action is persistent—the gum vehicle “reservoir” serving to release the medicament slowly at a rate roughly paralleling the drug's solubility in saliva.

The product is stable and retains its full potency under all ordinary conditions.

Supplied in packages of 24 tablets— $3\frac{3}{4}$ grs. (0.25 Gm.) per tablet—sanitaped, in slip-sleeve prescription boxes.

*A product of WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N.J.



White's

ulfathiazole gum

SAFE, TOPICAL CHEMOTHERAPY

Recent Advances In Feeding Newborns

Successful infant feeding depends on effective planning of the newborn's nutritional regimen. The first feeding, 12 hours after birth, consists of a prelacteal solution of KARO*. It is offered in one or two ounce amounts at two hour intervals for 24 to 48 hours to fulfill the high water requirement during the first week of life. Breast feeding may be initiated on the second day for five minute intervals to obtain colostrum and stimulate breast secretion. But the prelacteal feeding is continued immediately thereafter and between nursings.

Artificial feeding is offered on the second day if breast feeding is denied. Small infants are fed at 3 hour intervals and large infants at 4 hour intervals. The initial formula is a low caloric milk mixture to enable gradual adaptation of the feeding to the infant's tolerance. This is gradually concentrated at intervals of several days in the absence of digestive disturbances. The infant should be fed in a semi-reclining

position, burped during and after feeding, and kept on his right side or abdomen undisturbed for an hour.

The problems of newborns are always the same but the solutions differ with each era. Today the carbohydrate requirement of newborns is fulfilled by KARO as adequately as a generation ago. And, whatever the type of milk adapted to the infant's tolerance, KARO may be added confidently because it is a balanced mixture of low sugars, free flowing, well tolerated, hypo-allergic, resistant to fermentation, non-laxative and easily assimilated.

MEDICAL DIVISION
CORN PRODUCTS REFINING CO.
17 Battery Place, New York 4, N. Y.

*KARO is a registered trade-mark distinguishing this product of the Corn Products Refining Co., New York, N. Y.



R FIRST FORMULAS FOR NEWBORNS ADAPTED ACCORDING TO TOLERANCE

FORMULA I.....11 cal./oz.
*Whole milk..... 8 oz.
Water..... 12 oz.
Karo..... 1/2 oz.
3 1/2 oz. x 6 q 4h.

FORMULA I.....12.5 cal./oz.
**Evap. milk..... 4 oz.
Water..... 14 oz.
Karo..... 1/2 oz.
3 1/2 oz. x 6 q 4h.

FORMULA I.....11 cal. oz.
Dried milk..... 4 tbsp.
Water..... 20 oz.
Karo..... 1/2 oz.
3 1/2 oz. x 6 q 4h

FORMULA II.....13.5 cal./oz.
Whole milk..... 9 oz.
Water..... 11 oz.
Karo..... 3/4 oz.
3 1/2 oz. x 6 q 4h.

FORMULA II.....16 cal./oz.
Evap. milk..... 5 oz.
Water..... 13 oz.
Karo..... 3/4 oz.
3 oz. x 6 q 4h.

FORMULA II.....14.5 cal./oz.
Dried milk..... 5 tbsp.
Water..... 20 oz.
Karo..... 3/4 oz.
3 1/2 oz. x 6 q 4h.

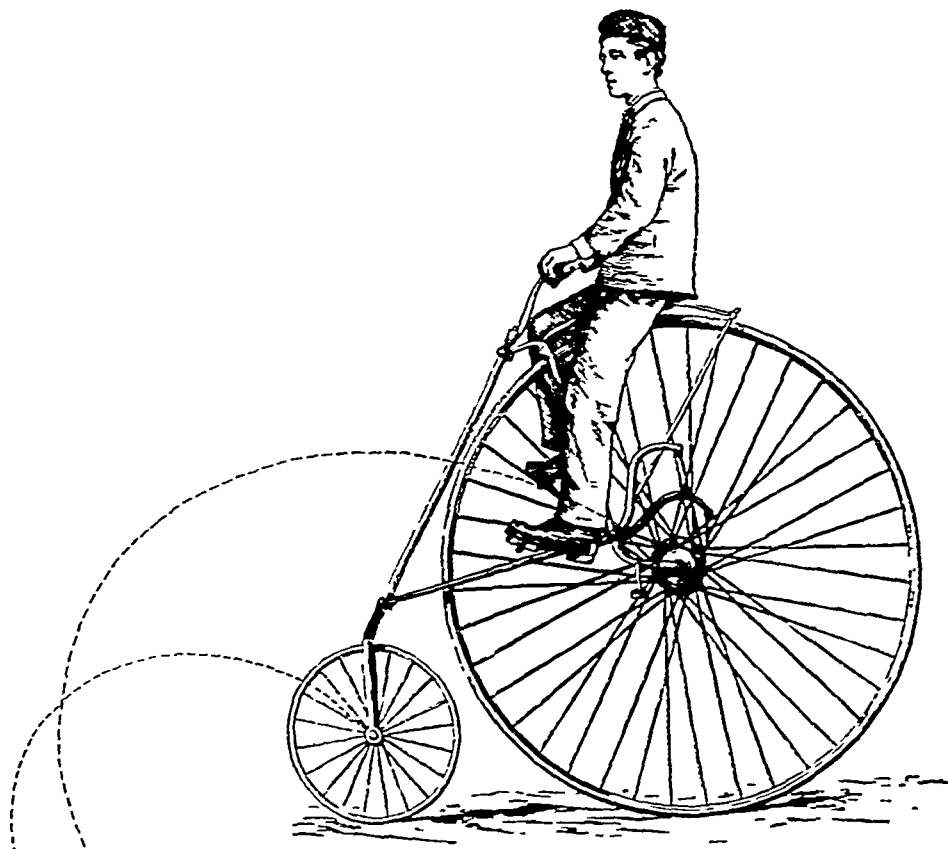
FORMULA III.....16 cal./oz.
Whole milk..... 10 oz.
Water..... 10 oz.
Karo..... 1 oz.
3 1/2 oz. x 6 q 4h.

FORMULA III.....20 cal./oz.
Evap. milk..... 6 oz.
Water..... 12 oz.
Karo..... 1 oz.
3 oz. x 6 q 4h.

FORMULA III.....18 cal./oz.
Dried milk..... 6 tbsp.
Water..... 20 oz.
Karo..... 1 oz.
3 1/2 oz. x 6 q 4h.

*Whole lactic acid milk formulas may also be prepared from whole cow's milk.

**Whole lactic acid milk formulas may also be prepared from evaporated cow's milk.



- He too can afford a Unicap* a day... only 2.7c**
- He too can *not* afford to be without the vitamin adequacy made simpler, more certain and more economical with a Unicap a day.

In the past 5 years 2.7c buys less and less food, less shelter and less clothes

BUT 2.7c buys more and more vitamins—all these

Vitamin A	5 000 U.S.P. units
Vitamin D	500 U.S.P. units
Ascorbic Acid (C)	37.5 mg.
Thiamine Hydrochloride (B ₁)	2.5 mg.
Riboflavin (B ₂)	2.5 mg.
Pyridoxine Hydrochloride (B ₆)	0.5 mg.
Calcium Pantothenate	50 mg.
Nicotinic Acid Amide (Nicotinamide)	200 mg.

Upjohn

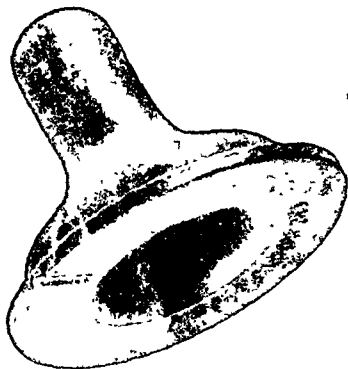
ESTABLISHED 1866 Kalamazoo, Michigan

FINE PHARMACEUTICALS SINCE 1886

in **a Unicap a day**

*Trademark for U.S.P. Off. **Actual cost in the most economical lot of 2,700 capsules also in lot cost units of 100 and 25

A truly important development in infant-feeding—



THE NEW

Bluebird
NURSER

THE NEW BLUEBIRD NIPPLE* offers all these "never-before" advantages:

- completely resistant to all oils.
- will not soften, swell or stretch through use or sterilization.
- feeding orifices remain uniform for the life of the nipple — one set should last entire bottle-feeding period.
- texture is firm, flesh-like, designed to stimulate sucking.
- resistant to temperatures that will destroy rubber nipples.

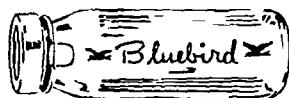
* made of Flecton—a new, tough, oil-resistant, dense material of low porosity, with tensile strength and tear-resistance many times that of natural rubber.



Ready for Feeding



Ready for Storage



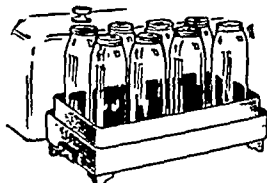
Leakproof In Any Position
May Be Stored On Side



The Bluebird Sealer Disc is wafer-thin metal, completely heat-resistant in sterilization, unbreakable.



The Bluebird Retainer Cap holds nipple firmly in place. Slight twist of cap acts on non-reversible nipple valve to regulate flow of milk as desired.



The Bluebird Bottle is Slo-Annealed Glass to afford lowest possible breakage and freedom from toxic materials sometimes found in glass.



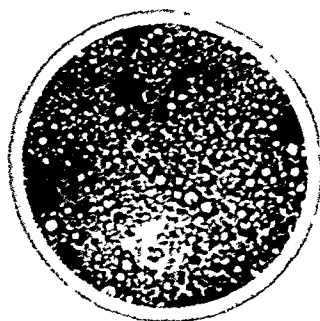
Bluebird NURSER • COSHOCTON, OHIO

In the hospital or home— LOTION GUARDS BABY SKIN BETTER



Miliaria incidence lower, hospitals find. New Johnson's Baby Lotion was hospital-tested on newborn infants for two years. Records showed an impressive drop in the incidence of miliaria with routine use of Lotion. Over 1400 hospitals have changed to Johnson's Baby Lotion for regular skin care.

Discontinuous film of
Johnson's Baby Lotion, showing
micron-size oil globules (1000x.)



Lotion ideal for home use. No special technique is necessary for applying Johnson's Baby Lotion—the mother uses it exactly like baby oil. Since Lotion affords *extra protection against rashes*, more and more doctors are recommending it for use under home conditions.

Infant skin can function normally. Johnson's Baby Lotion is a homogenized emulsion of

mineral oil and lanolin in water, with a mild antiseptic—hydroxy quinoline—added. As the water phase evaporates, a *discontinuous film* of micron size oil globules (see photomicrograph) is left.

This permits normal heat radiation and allows perspiration to escape readily, thus lessening the danger of irritation.



JOHNSON'S BABY LOTION

Johnson & Johnson

FREE! Mail coupon for 12 distribution samples!

Johnson & Johnson, Baby Products Division
Dept. A-2, New Brunswick, N. J.

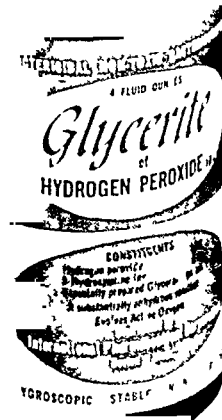
Please send me, free of charge, 12 distribution samples of Johnson's Baby Lotion.

Name

Street

City State

Offer limited to medical profession in U.S.A.



CONSTITUENTS:
Hydrogen peroxide (90%)
2.5%
8-Hydroxyquinoline 0.1%
Especially prepared glycerol
qs. ad 120cc.
Supplied in four ounce
bottles

Pediatrician reports:

"Babies were in a better physical condition"* with Swift's Strained Meats



In recent test feedings,* six-weeks-old infants received a meat supplement in their formula which increased the protein content 25%. In the opinion of the pediatrician in charge, the meat-fed babies were in a better physical condition than babies receiving the same formula with no meat added. Nurses reported that infants who received meat were more satisfied and slept better. This study, using Swift's Strained Meats, further indicated that meat not only checks the drop in hemoglobin, characteristic of this age, but actually promotes hemoglobin and cell formation.

100% meat—soft and smooth for earlier meat-feeding

Specially prepared in particles fine enough for formula-feeding, Swift's Strained Meats facilitate introducing meat *earlier in life*. They offer an abundance of complete, high-quality proteins needed to support the infant's rapid growth. Swift's Strained Meats provide a rich source of thiamine, niacin, riboflavin and iron. The six kinds of Swift's Strained Meats differ in taste and texture from baby's other solid foods—help him form nutritionally sound eating habits. The variety includes: beef, lamb, pork, veal, liver and heart. Each is 100% meat, ready to heat and serve.

Also Swift's Diced Meats

Bite-size tender meats—firm enough to encourage chewing. Swift's Diced Meats offer tempting flavors that help prevent anorexia in the older baby and young child.



For further information, write Swift & Company, Dept. SMB, Chicago 9, Illinois.



All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association.

*MEAT IN THE DIET OF YOUNG INFANTS
E. M. Livingston, Ph.D., and George Clark, M.D.
Journal of the American Medical Association
U.S.A. 134 1215, August 9, 1947

SWIFT...foremost name in meats...first with 100% Meats for Babies

*The Patient's
Food Tray
As a Factor in
CONVALESCENCE*



To fulfill its function, the patient's meal should have three qualities. It should be easily assimilated. It should look inviting. And it should taste good, to lift the appetite.

On all three counts, dishes made with Knox Gelatine fit into this picture. Knox, of course, is all real gelatine, no sugar, unlike the artificially-flavored, acidified gelatine powders, which are $\frac{7}{8}$ sugar and only $\frac{1}{8}$ gelatine. So it is well to specify Knox by name.

With Knox Gelatine a limitless variety of tempting dishes can be made—many that include real fruits, vegetables and fresh, natural juices with their vitamins and minerals.

In special dietaries this plain gelatine provides an excellent vehicle as well as a useful protein supplement.

Free Booklet—"Feeding the Sick and Convalescent" will be sent to you on request. Address Knox Gelatine, Dept. O-2, Johnstown, N. Y.



Two Sizes—1 oz. (4 envelopes)
and $\frac{1}{2}$ lb. (32 envelopes)

KNOX
Gelatine
U. S. P.

All Protein—No sugar

WHEN SENSITIVITY TO COW'S MILK LACTALBUMIN IS SUSPECTED

Meyenberg Evaporated GOAT MILK

THE SUPERIOR-QUALITY
NATURAL MILK FOR
INFANTILE ECZEMA
AND DIFFICULT
FEEDING CASES



MEYENBERG Evaporated Goat Milk has gained outstanding national acceptance because it is *uniform, sterile and more palatable*. Prescribe or recommend Meyenberg whenever Cow's Milk allergy is suspected.



Available in 14-ounce hermetically-sealed containers
at all pharmacies

Now
Available
in
Unlimited
Quantities

Advertised only to
the medical profession

SPECIAL MILK PRODUCTS, INC.

11500 TENNESSEE AVENUE • LOS ANGELES 25, CALIFORNIA

A Better Nutritional Start For The Day

Despite the unanimous agreement among all nutritionists and dietitians that breakfast should provide from one-fourth to one-third of the daily caloric and nutrient needs, a large segment of our population fails to eat an adequate morning meal. Not only adults, but also children of school age are guilty of this practice which is bound to decrease morning acuity and stamina, and to impose an almost impossible burden upon the other two meals to overcome the deficit created.

A widely endorsed basic breakfast pattern provides the foundation upon which a better nutritional start for the day can be built. Supplying fruit, cereal, milk, bread and butter, it contributes 611 calories and virtually all essential nutrients in generous amounts. The cereal serving, consisting of hot or ready-to-eat breakfast cereal, milk, and sugar, is the main dish of this meal. It supplies significant amounts of the nutrients provided by the breakfast, and adds both taste appeal and variety.

The table indicates the nutrient values of this basic breakfast and the contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk and 1 teaspoonful of sugar.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

BASIC BREAKFAST

Orange juice, 4 oz.;
Ready-to-eat or
Hot Cereal, 1 oz.;
Whole Milk, 4 oz.;
Sugar, 1 teaspoon;
Toast (enriched,
white), 2 slices;
Butter, 5 Gm.
(about 1 teaspoon)
Whole Milk, 8 oz.

TOTALS supplied by Basic Breakfast

CALORIES..... 611
PROTEIN..... 20.7 Gm.
CALCIUM..... 0.465 Gm.
PHOSPHORUS .. 488 mg.
IRON..... 3 mg.
VITAMIN A..... 1074 I.U.
THIAMINE..... 0.52 mg.
RIBOFLAVIN..... 0.87 mg.
NIACIN..... 2.3 mg.
ASCORBIC ACID .. 64.8 mg.

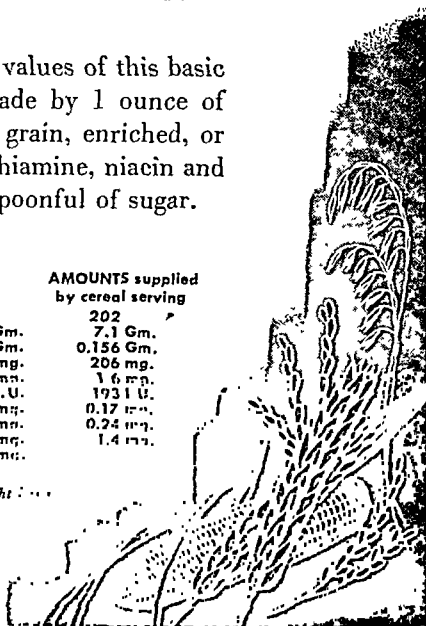
AMOUNTS supplied by cereal serving

202
7.1 Gm.
0.156 Gm.
206 mg.
1.6 mg.
193 I.U.
0.17 mg.
0.24 mg.
1.4 mg.

*Composite average of all breakfast cereals on dry weight basis

CEREAL INSTITUTE, INC.

A research and educational endeavor devoted to the betterment of national nutrition.
135 South La Salle Street • Chicago 3



NOW—for the FIRST TIME!

This new treatise, *The Development of the Infant Mouth from Embryo through First Year*, represents the research of practicing surgeons in hospitals and clinics, professors in medical and dental colleges, dental clinicians, an author and lecturer on embryology, a physicist, an anatomist, and the director of an eye and ear infirmary.

Here are six of forty illustrations in the diagrammatic, full-color, four-fold chart on prenatal and post-natal development. All but one of the drawings were made directly from dissection. The X-ray plates were taken solely for the treatise.



Specimens were collected over a period of eight months from the pathology departments of general, lying-in and children's hospitals, plus a medical college. These and other important findings constitute a valuable addition to your reference library.

FOR YOUR COMPLIMENTARY COPY, fill out and send in the coupon! (This offer is limited to doctors and nurses only.)

DAVOL

DAVOL RUBBER COMPANY
PROVIDENCE 2, RHODE ISLAND

Davol Rubber Company
Department JP8-3
Providence 2, Rhode Island

Please send me your new treatise "The Development of the Infant Mouth from Embryo through First Year."

Name.....

Address.....

City..... State

Wyeth

PHILADELPHIA 3, PA.

(9)

S-M-A[®] builds husky babies

Protein in S-M-A is complete and adequate. It is present in the same proportion as in breast milk. Protein in S-M-A is utilized for growth.

Because the fat and carbohydrate in S-M-A are perfectly balanced (as in human milk) to supply necessary energy, the protein element in the formula is available for its own special purpose—the building of tissue. Thus growth factors are not robbed to supply caloric requirements.

S-M-A closely approximates mother's milk.

The S-M-A formula is well suited to modification, as the physician may wish, for special feeding problems.



The Tar Preparation... THAT NEVER ENCOUNTERS PATIENT RESISTANCE

Tarbonis
is widely prescribed in

- Eczema
- Psoriasis
- Ringworm
- Occupational Dermatitis
- Folliculitis
- Seborrheic Dermatitis
- Intertrigo
- Pityriasis
- Pruritus
- Tinea Cruris

In 2 1/4 oz., 8 oz., 1 lb.
and 6 lb. jars.

When infection supervenes, SUL-TARBONIS combines the bactericidal properties of sulfathiazole (five per cent) with the virtues of Tarbonis.

RARE INDEED would be the physician who has not encountered patient resistance to tar preparations. The objectionable odor, the staining and soiling of skin, linen and clothing, the unsightly appearance on exposed body surfaces, whether the preparation be white or the blackish-brown tar color, have proved serious stumbling blocks in the use of tar, regardless of its high therapeutic efficacy in a host of frequently seen conditions.

In Tarbonis, an alcoholic extract of carefully selected tars (5 per cent) incorporated together with lanolin and menthol in a vanishing-type cream, this therapeutic efficacy is fully preserved, but all objectionable features are overcome.

Tarbonis leaves no trace on the skin, requires no removal before reapplication. It is free from all tarry odors, instead presents a pleasant soapy scent. It is greaseless, nonstaining, and nonsoiling—not only to skin but to linen and clothing as well.

Since Tarbonis is nonirritant even to the tenderest skin, it may be applied as often as desired, thus assuring a high degree of clinical success.

Physicians are invited to send for professional sample.

THE TARBONIS COMPANY

4300 Euclid Avenue • Cleveland 3, Ohio

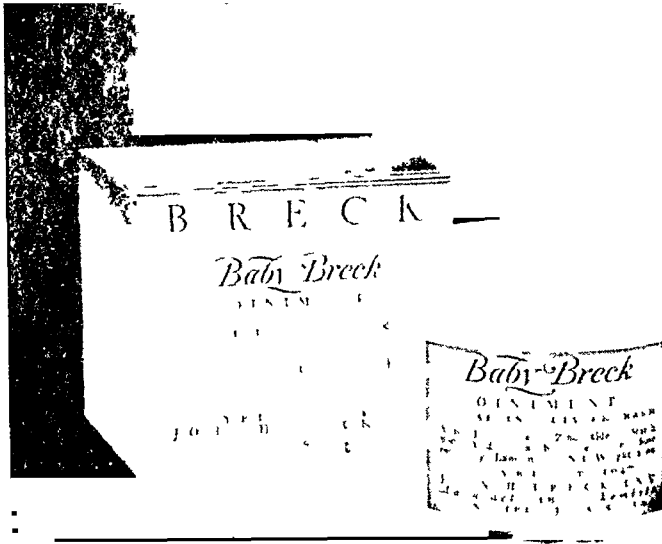
TARBONIS COMPANY,
Cleveland 3, Ohio

You may send me a sample of Tarbonis.

Dr. _____

Address _____

City, Zone, and State _____



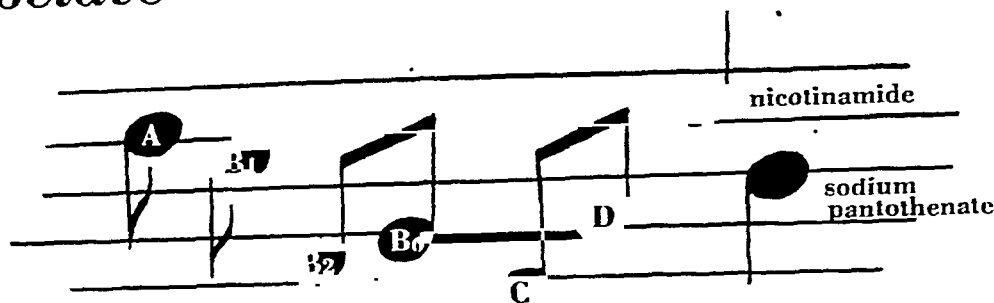
Baby Breck

OINTMENT For Aiding Diaper Rash

Baby Breck Ointment was made to ease the discomfort of diaper rash. Its mild, bland ingredients minimize the chance of any allergic reaction. Baby Breck Ointment forms a moisture resistant coating on the skin that is especially helpful during the night. This ointment may be used on other chafed areas of the skin.

Active ingredients—zinc oxide, starch, boric acid in a bland emollient base containing lanolin
 JOHN H. BRECK, INC. MANUFACTURING CHEMISTS—SPRINGFIELD, MASSACHUSETTS
 CANADIAN ADDRESS: 310 ST. PATRICK STREET, OTTAWA

“octave”



*concerted action of 8 vitamins
when you prescribe*

ABDEC[®] drops

ABDEC DROPS, in harmony with their wide range of therapeutic and prophylactic indications, supply eight important vitamins in a clear, non-alcoholic solution—vitamins A, B₁, B₂, B₆, C, D, nicotinamide and sodium pantothenate. They are used most effectively for the infant in the first crucial months of existence and for the growing child.

ABDEC DROPS may be placed directly on the tongue or added to milk, fruit juices, soups, cooked or pre-cooked cereals and other foods. The full daily dose is preferably given at a single feeding. The average daily dose for infants under one year is 0.3 cc. (5 minims); for older children, 0.6 cc. (10 minims).

ABDEC DROPS are supplied in 15-cc. and 50-cc. bottles with a special graduated dropper to facilitate accurate dosage.

Each 0.6 cc. (10 minims) of ABDEC DROPS contains vitamin A, 5000 units; vitamin D, 1000 units; vitamin B₁, 1 mg.; vitamin B₂, 0.4 mg.; vitamin B₆, 1 mg.; pantothenic acid (as sodium salt), 2 mg.; nicotinamide, 5 mg.; vitamin C, 50 mg.

PARKE. DAVIS & COMPANY • DETROIT 32, MICHIGAN

ABDEC

Why do Sally, Irene and Mary need vitamin D

?

Growing children require vitamin D mainly to prevent rickets. They also need vitamin D, though to a lesser degree, to insure optimal development of muscles and other soft tissues containing considerable amounts of phosphorus . . .

Milk is the logical menstruum for administering vitamin D to growing children, as well as to infants, pregnant women and lactating mothers. This suggests the use of Drisdol in Propylene Glycol, which diffuses uniformly in milk, fruit juices and other fluids.

Average daily dose for infants 2 drops, for children and adults 4 to 6 drops, in milk. Available in bottles of 5, 10 and 50 cc. with special dropper delivering 250 U.S.P. units per drop.



DRISDOL IN PROPYLENE GLYCOL

MILK DIFFUSIBLE VITAMIN D PREPARATION
ODORLESS • TASTELESS • ECONOMICAL

DRISDOL, trademark Reg. U. S. Pat. Off.
& Canada, Brand of Crystalline Vitamin D₂
(calciferol) from ergosterol

Winthrop Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

The businesses formerly conducted by Winthrop Chemical Company Inc.
and Frederick Stearns & Company are now owned by Winthrop Stearns Inc.

Pediatricians Know Young Bones Need Proper Support - *without restraint!*

JUMPING-JACKS
SOFT SHOES FOR HARD WEAR
For Children 6 Months to 4 Years Old



JUMPING-JACKS

THE MOST IMPORTANT
DEVELOPMENT IN
CHILDREN'S SHOES
IN OVER **50** YEARS

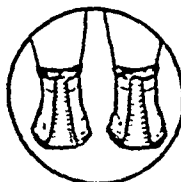
HUNDREDS OF LETTERS OF PRAISE

Every mail brings JUMPING-JACK "fan" letters from all over the country. Mothers, aunts, uncles, grandparents, doctors—they all write in to tell us of how happy they—and more important, their child or children—are with JUMPING-JACK Shoes.



PREVENTS FRICTION RETAINS SHAPE

Number one (left) shows cramped foot and friction due to improper balance. Number two (right) shows foot freedom and equal distribution of weight.



BUILDS CONFIDENCE FOR "FIRST STEPS"

Patented Jumping-Jacks help prevent ankles from turning... assure more healthful walking from the start. Extra satisfaction assured by superior craftsmanship and materials.

VAISEY-BRISTOL SHOE COMPANY, INC.
625 SOUTH GOODMAN STREET • ROCHESTER 7, N. Y.

Pleasant "Salivary Analgesia" in



Pharmaceutical Manufacturers, Newark 7, N. J.

Sore Throat...Fever...Headache...Tonsillitis

Widely used for its prolonged analgesic action in post-tonsillectomy care and pharyngitis, Aspergum has also proved a pleasant, easy method of administering aspirin for its analgesic-antipyretic effect in the common cold and other non-specific febrile conditions.

The palatable chewing gum base of Aspergum is particularly appealing to children. Each tablet of Dillard's Aspergum contains $3\frac{1}{2}$ grains of aspirin.

Ethically promoted. In packages of 16; moisture-proof bottles of 36 and 250.

Dillard's

sp ergum

SALIVARY ANALGESIA-PLUS

Articles to appear in early issues of

THE JOURNAL OF PEDIATRICS

SUBLINGUAL METHYL TESTOSTERONE FOR BOYHOOD EMOTIONAL, PHYSICAL, AND GENITAL IMMaturity.

By Floyd E. Harding, M.D., Los Angeles, Calif.

PEDIATRIC DEATHS IN A LARGE GENERAL HOSPITAL.

By R. V. Platou, M.D., John Kometani, M.D., and Norman Woody, M.D., New Orleans, La.

NON-TUBERCULOUS PULMONARY CALCIFICATION.

By Alfred D. Biggs, M.D., and Ralph G. Rigby, M.D., Chicago, Ill.

STUDY OF HUNGER EDEMA IN CHILDREN.

By Lythymios P. Petrides, M.D., Athens, Greece.

UNIFORM ERUPTION OF KAPOSI DUE TO VACCINIA VIRUS COMPLICATING ATOPIC ECZEMA.

By Joseph H. Fries, M.D., Stanford Borne, M.D., and Harold L. Barnes, M.D., Brooklyn, N. Y.

CHRONIC MENINGITIS TREATED WITH STREPTOMYCIN.

By Otto S. Nau, Jr., M.D., and Francis J. Wenzler, M.D., Boston, Mass.

PROCTOLOGIC EXAMINATION OF INFANTS AND CHILDREN.

By Saul Schapiro, M.D., Brooklyn, N. Y.

ALKALIGENES FECALIS BACTEREMIA AND MENINGITIS.

By Harold W. Bischoff, M.D., Adrian Recinos, Jr., M.D., William S. Anderson, M.D., and E. Clarence Rice, M.D., Washington, D. C.

TIME ELEMENT IN THE DEVELOPMENT OF IRREVERSIBLE BRONCHIECTASIS.

By David M. Spain, M.D., and Charles W. Lester, M.D., New York, N. Y.

THE USE OF BENZEDRINE AND DEXEDRINE SULFATE IN THE TREATMENT OF EPILEPSY.

By Samuel Livingston, M.D., Laslo Kajdi, M.D., and Edward M. Bridge, M.D., Baltimore, Md.

HOMOLOGOUS SERUM HEPATITIS.

By J. Buren Sidbury, M.D., and Rowena Sidbury Hall, M.D., Wilmington, N. C.

DIAGNOSIS AND SURGICAL TREATMENT OF CERTAIN CONGENITAL CARDIOVASCULAR ANOMALIES.

By Merl J. Carson, M.D., and Thomas H. Burford, M.D., St. Louis, Mo.

AN EVALUATION OF THE PENICILLIN TREATMENT IN EARLY CONGENITAL SYPHILIS.

By Leslie Paxton Barker, M.D., New York, N. Y.

RELATIONSHIP OF RACE TO THE INCIDENCE OF DIPHTHERIA AND TO SCHICK, TUBERCULIN, AND WASSERMANN TESTS IN HOSPITALIZED CHILDREN.

By David W. Martin, M.D., and Jay M. Arena, M.D., Durham, N. C.

CANDIDA ALBICANS INFECTION IN A CHILD.

By C. F. Engelhard, M.D., Rotterdam, Holland.

RECEDING CHIN AND GLOSSOPTOSIS.

By Aaron Nisensohn, M.D., Los Angeles, Calif.

LACK OF CORRELATION BETWEEN POSSIBLE RH INCOMPATIBILITY AND MONGOLIAN IDIOCY.

By Hans Meyer, M.D., Crownsville, Md.

NEW CONCEPTS OF OSTEOMYELITIS IN THE NEWBORN INFANT.

By Charles G. Hutter, Jr., M.D., Los Angeles, Calif.

TETANUS NEONATORUM.

By John R. Harvin, M.D., W. D. Hastings, Jr., M.D., and C. R. F. Baker, M.D., Sumter, N. C.



Children got an itch

Cause may be multiple, prompt symptomatic relief is singularly simple. Calanol Ointment, containing camphorated chloral and hyoscyamine oleate, is a particularly safe, exceedingly bland antipruritic for pediatric practice.

The danger of infection of excoriated and contaminated lesions is minimized. A healthy rapport between little patient and physician is established and paves the way for the cooperation essential to continued investigations and elimination of etiologic factors.

FIRST THOUGHT IN PEDIATRIC PRURITUS

Thos. Leeming & Co. Inc.

155 EAST 44TH STREET, NEW YORK 17, N.Y.



Wouldn't YOU
smile too
if...

... all babies took to their first cereal the way this young enthusiast takes to his Gerber's?

Of course, more babies would balk less if their mothers took your advice about starting slowly—with small quantities of cereal diluted to almost liquid consistency.

And more mothers and doctors would have less trouble with baby's first solid food after milk, if baby liked the *texture* and *taste* of his cereal. So, with that in mind, may we point out that

90% OF THE BABIES WHO START ON GERBER'S CEREALS STAY WITH THEM (according to a recent survey). *Finely strained* Gerber's Cereal Food, Strained Oatmeal and Barley Cereal are so good-tasting. They give baby appetite-tempting variety—plus *added iron, calcium, and B-complex vitamins*. And, Gerber's are so low priced—from Cereals through Strained and Junior Foods.



FREE SAMPLES of Gerber's ready-to-serve Cereals—plus professional reference cards. Write to Gerber's, Dept. 273-8, Fremont, Mich.

Gerber's

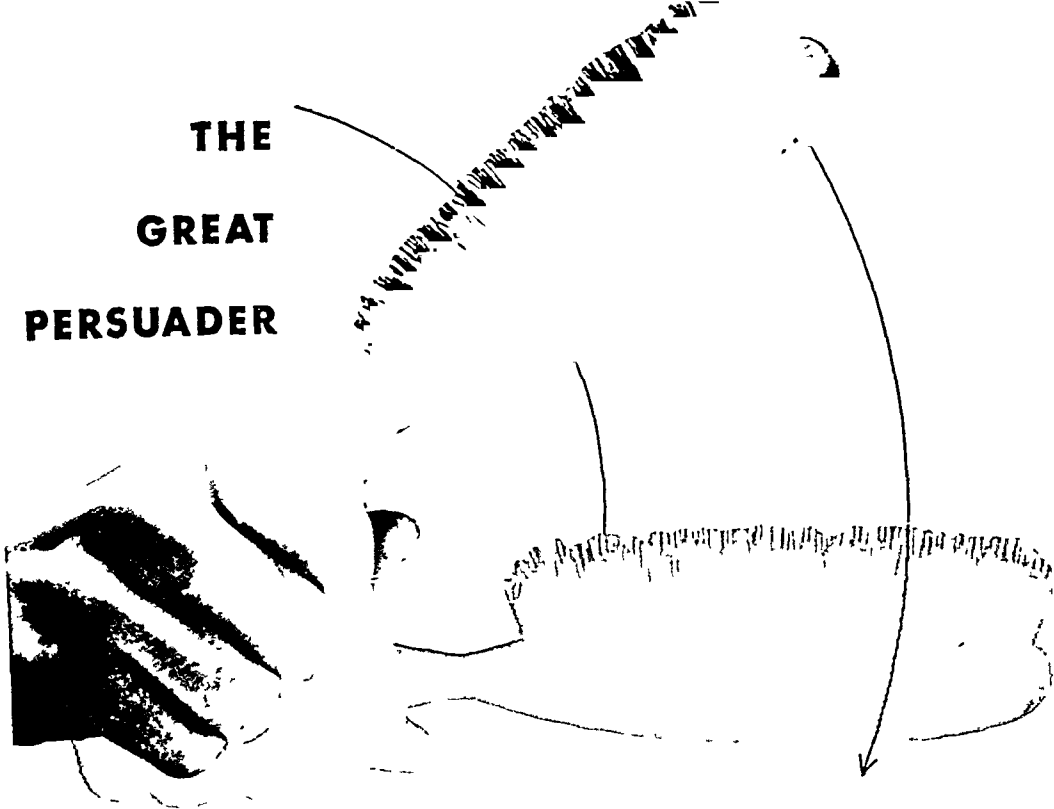
BABY FOODS

FREMONT, MICH

OAKLAND CAL

3 CEREALS • 18 STRAINED FOODS • 13 JUNIOR FOODS

THE GREAT PERSUADER



All too often irate parents resort to a "good licking" for children who refuse to eat. The therapeutic merits of such a procedure are of course not medically recognized, since anorexia often is more than a stubborn personality defect.

More effective than punishment is the stimulation of B complex on appetite. 'Ryzamin-B' No. 2 has proved especially effective because of a pleasant taste-appeal which children relish. Containing the *natural* B complex as a concentrate of *Oryza sativa* (American rice) polishings, 'Ryzamin-B' No. 2 is also potently fortified with synthetic B factors. Children enjoy its rich, honey-like flavor any way it is given—right from its special measuring spoon, as a delicious spread with jam or peanut butter, or dissolved in milk, fruit juice and other beverages

'RYZAMIN-B' NO. 2

BRAND RICE POLISHINGS CONCENTRATE

WITH ADDED THIAMINE HYDROCHLORIDE, RIBOFLAVIN AND NICOTINAMIDE
TUBES OF 2 OZ. AND BOTTLES OF 8 OZ.

'Ryzamin-B' registered trademark



BUFFOURGH'S WELLCOME & CO. (U.S.A.) INC. 9 & 11 EAST 41ST STREET, NEW YORK 17

March, 1949



No other crop could grow here



The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



Vast areas of the country would have to be considered wasteland, so far as human nutrition is concerned, were it not for the ability of livestock to feed on the grasses and roughage growing in the many areas which do not lend themselves to cultivation.

Our livestock population turns many plants, in themselves inedible by man, into meat . . . man's preferred protein food.

Thus livestock makes land, which otherwise would be useless for human nutrition, produce an outstanding protein food for man. This is of added importance today because of the world-wide scarcity of high-quality protein foods.

AMERICAN MEAT INSTITUTE

MAIN OFFICE, CHICAGO . . . MEMBERS THROUGHOUT THE UNITED STATES

To Save Your Time



**SAMPLE
COPY
ON REQUEST**

GIVE NEW MOTHERS

FREE

Daily Guide Book

Written under direction of
a leading pediatrician, by
Phyllis Krafft Newill.

"Bringing Up Baby" is free for distribution to your patients. It covers the pre-natal period up through the "romper" age, with special emphasis on feeding, care and training. Read and approved by physicians before publication

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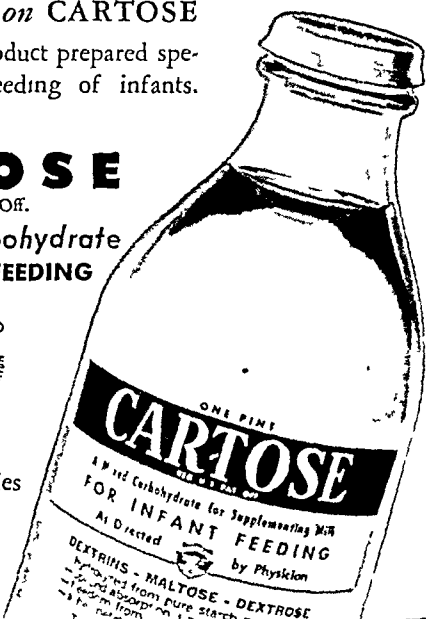
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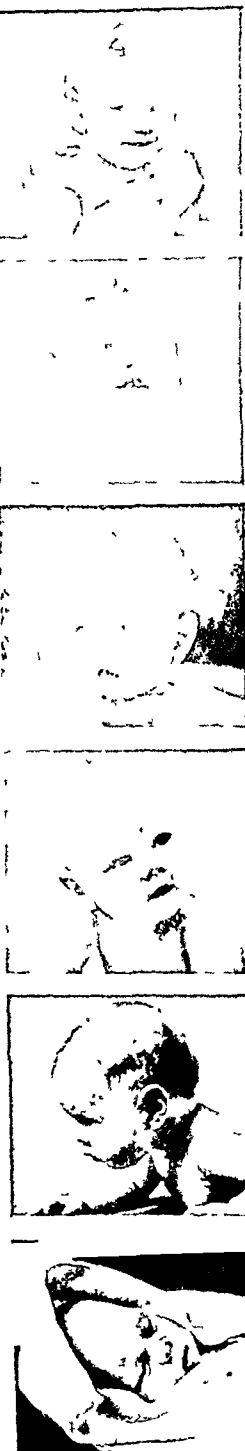


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Original Communications

RESPIRATORY ACIDOSIS AND ALKALOSIS IN CHILDREN

SAMUEL SPECTOR, M.D., AND CHARLES F. MCKHANN, M.D.
CLEVELAND, OHIO

DISTURBANCES of acid-base balance are associated with numerous disorders of infancy and childhood, and acidosis or alkalosis may account for much of the symptomatology which a patient presents. Restoration to normal of acid-base relationships may be a necessary part of the treatment of seemingly unrelated diseases.

We have been impressed by the incidence in childhood of respiratory acidosis and alkalosis, conditions well defined by the chemist and physiologist but all too often not recognized by the clinician.¹ To clarify the relationships of respiratory acidosis and alkalosis to other types of acid-base disturbances in infancy and childhood, a brief review of the control of the chemical reaction of body fluids may be helpful.

The chemical reaction of fluids in the body may be influenced by the absorption of nutriment and fluids from the gastrointestinal tract; the losses of water, electrolytes, and tissue waste products through the kidneys; losses of water and carbon dioxide through the lungs; and the losses of water, electrolytes, and waste products through the skin. Uptake or loss through these organs affects the composition of blood plasma and, secondarily, of the interstitial fluids. The chemical conditions within the body cells must then be mediated through exchange of metabolic materials between the cells and the surrounding extracellular fluids. The environment of the cells is of remarkably constant composition and of a chemical reaction which various mechanisms serve to defend at pH 7.4.

The factors which influence reaction in blood plasma are controlled largely by renal function with the exception of the plasma content of carbonic acid which is controlled by the respiratory mechanism. The mechanism by which the plasma protein level is maintained is not known. A diagram devised by Gamble² illustrates the relationship of the principal components of the plasma acid-base system, together with their concentrations in plasma water (Chart 1). In listing the relative values of cations on the left and anions on the right, it is emphasized that in the body fluids we are dealing not with salts but with separate amounts of individual ions. The small amount of free carbonic acid

From the Department of Pediatrics, Western Reserve University School of Medicine, and The Babies and Childrens Hospital of Cleveland.

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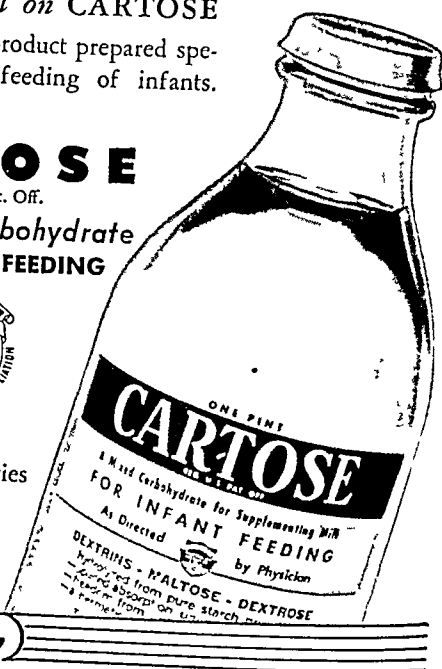
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on top of the diagram is not completely separated into its component ions because it is only slightly dissociated. From this chart it may be noted that sodium constitutes about 91 per cent of the base while the chloride ion is the largest component, 66 per cent, of the total acid value. The next largest item of acid structure is the concentration of bicarbonate ion (HCO_3^-), which is determined by the base in excess over the amount needed to balance the acid ions which, except for protein, are under renal control. Thus, the B.HCO_3 is indirectly under renal regulation; this is in distinction to the H.HCO_3 which is chiefly under respiratory control.

Of the various buffer systems in the blood, the free carbonic acid-base covering bicarbonate $\frac{\text{H.HCO}_3}{\text{B.HCO}_3}$ buffer is one of the most important and is fortunately easy to determine by laboratory methods. Total plasma carbon-dioxide content is a measure of carbonic acid (H.HCO_3), normally 3 volumes per cent or 1.35 meq. per liter plus the bicarbonate covering the base (B.HCO_3), normally 60 volumes per cent or 27 meq. per liter. From the normal figures for these two CO_2 components, it is evident that total CO_2 content reflects largely the B.HCO_3 content of the plasma.

The H.HCO_3 and B.HCO_3 are normally maintained in the blood within narrow limits in a ratio of 1:20. At this ratio, the dissociation constant is such that the plasma pH is 7.4, pH being equal to 6.1 plus $\log \frac{\text{B.HCO}_3}{\text{H.HCO}_3}$ (Henderson-Hasselbalch equation). The pH varies inversely with change in the ratio. An uncompensated increase in B.HCO_3 , that is, an increase in B.HCO_3 without a relative increase in H.HCO_3 , produces an increase in pH and an uncompensated alkalosis; an uncompensated decrease of B.HCO_3 produces a fall in pH, and an uncompensated acidosis. Uncompensated increase or decrease in the H.HCO_3 as observed secondary to derangement of the respiratory mechanism produces the opposite effect. As long as the ratio of 1:20 is maintained, changes in carbonic acid or bicarbonate do not alter the pH. Thus, there can be compensated acidosis or alkalosis with marked change in alkali reserve and little deviation of plasma pH from normal. The efficiency of the $\frac{\text{H.HCO}_3}{\text{B.HCO}_3}$ buffer system is dependent largely on the ability of the body to maintain it at a ratio of 1:20. The immediate defense of this ratio is primarily a function of the control of H.HCO_3 by the respiratory mechanism, and the first sign of an alteration in plasma pH is usually seen in rate and depth of respirations, since the concentration of carbonic acid in the blood is dependent upon the rate of formation of carbon dioxide in the body and of its removal from the blood by the lungs. For other anions and cations the mechanisms of absorption from the intestines and excretion by the kidneys largely determine the plasma levels. The concentration of base covering bicarbonate (B.HCO_3) is determined by the base which remains in excess after the union of plasma base with the anions of chloride, phosphate, sulfate, and organic acids, which are chiefly under renal control, and protein. Renal response to changes in electrolyte balance apparently is much slower in its effect than is the response of the respiratory mechanism.

For the kidneys to excrete an excessive amount of anions or cations and to re-establish acid-base equilibrium, a definitive water excretion is required and a considerable time component is involved, whereas the respiratory reaction to slight changes in plasma pH is prompt and is usually effective in preventing wide or sudden deviations from the normal. Respiratory acidosis or alkalosis develops when the respiratory mechanism to prevent plasma pH change functions inadequately.

ACID-BASE COMPOSITION OF BLOOD PLASMA

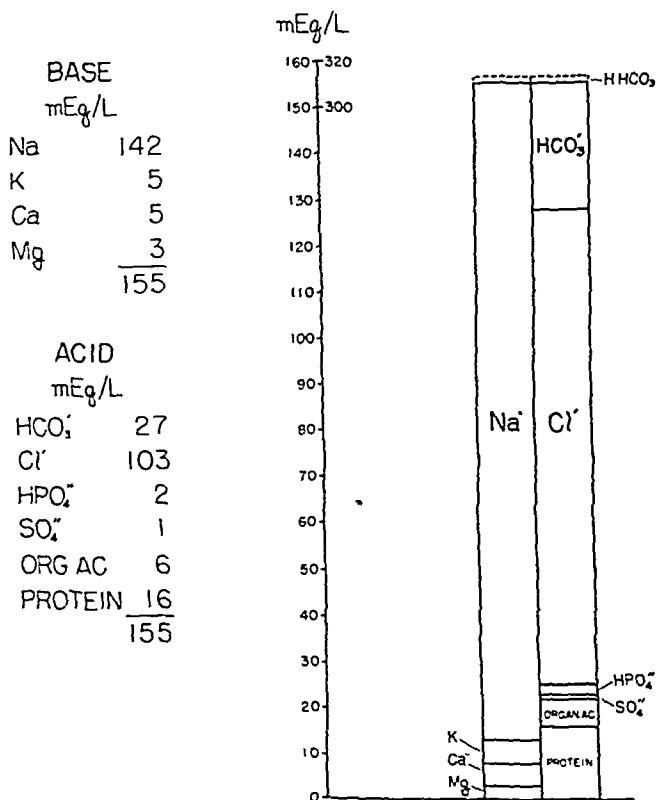


Chart 1.

CAUSES OF ACIDOSIS AND ALKALOSIS

Ordinarily, acidosis in infants and children is due to one of the following causes:

1. *Ketosis* due to accumulation of ketone bodies in the blood and tissue fluids with displacement of bicarbonate and chlorides, resulting in normal or lowered pH and lowered values of HCO₃⁻ and of Cl⁻, with normal base. Both the lungs and the kidneys participate in the compensatory action to make room in the plasma electrolyte structure for the abnormal acid. Ketosis is seen in starvation, in diabetes mellitus, in glycogen storage disease (Von Gierke's), and in the presence of acute infection.

2. *Renal acidosis* due to failure of renal function and to the accumulation of fixed anions in the blood plasma; probably also to base loss due to failure of ammonia production and subsequent drain on plasma cations. Infants and children with dehydration and subsequent anuria temporarily presenting the picture of renal acidosis outnumber patients with permanent renal injury.

3. *Gastrointestinal acidosis* due to the loss of base as in diarrheal disease or to the ingestion of acid-producing salts such as calcium chloride, ammonium chloride, or other fixed anions. With diarrheal disease, the resulting dehydration may cause superimposed renal acidosis.

Alkalosis in childhood may follow:

1. *Vomiting of gastric contents with Cl⁻ loss*, depletion of the chlorides of plasma and extracellular fluid, extension of bicarbonate in the plasma to balance this loss, and consequent disturbance of carbonic acid-bicarbonate buffer system with resultant high bicarbonate content of plasma and possibly an elevated plasma pH.

2. *Excessive ingestion of alkali*, especially sodium bicarbonate, which serves to increase the bicarbonate concentration of the plasma and may result in elevated pH.

The accompanying chart lists the common causes of acidosis and alkalosis together with the customary chemical measurements usually obtained in such cases (Chart 2).

The three types of acidosis mentioned all result in lowered total bicarbonate in the blood plasma, so we have become accustomed to think of acidosis as characterized by low plasma bicarbonate, and of high plasma bicarbonate as usually indicative of alkalosis. In general this is true, and reaction of blood plasma usually follows total bicarbonate concentration.

Also, in acidosis or alkalosis, as outlined previously, the primary alteration is in the B.HCO_3 and the respiratory mechanism is normal; and so in metabolic acidosis there occurs compensatory hyperventilation, producing loss of H.HCO_3 , and in metabolic alkalosis, shallow breathing which aids retention of H.HCO_3 . In this manner, in metabolic acidosis or alkalosis, the respiratory mechanism helps to maintain the $\frac{\text{H.HCO}_3}{\text{B.HCO}_3}$ in a ratio of 1:20, thus often inducing a compensated acidosis or alkalosis with little alteration of the normal plasma pH despite marked changes in the B.HCO_3 or alkali reserve.

In respiratory acidosis and alkalosis with derangement of the respiratory mechanism and primary alteration of H.HCO_3 rather than B.HCO_3 , prompt pulmonary defense of $\frac{\text{H.HCO}_3}{\text{B.HCO}_3}$ is impaired, compensation occurs slowly, and there may be a persistent alteration of plasma pH.

MECHANISM OF RESPIRATORY ACIDOSIS

Increased carbon-dioxide tension in the blood associated with respiratory acidosis has been observed to result from: (1) an increase of carbon dioxide in the alveolar air due to excessive carbon dioxide in the atmosphere; (2) obstruction to the escape of carbon dioxide from the alveoli, or (3) prevention

of the transport of carbon dioxide from the blood to the alveoli through the various states of asphyxia; and (4) following the suppression of respirations by effects on the central nervous system of drugs such as morphine and infections such as poliomyelitis.

Conditions interfering with the escape of carbon dioxide from the blood develop in patients with pulmonary edema (caused by toxic irritations, infections, or cardiac decompensation), pulmonary emphysema, and pulmonary fibrosis. In infancy we have observed carbon-dioxide retention in cases of emphysema due to extensive bronchiolitis, that is, a pathologic condition in which, because of inflammatory swelling and collections of thick, viscid mucus in the bronchioles, there was obstruction to the adequate escape of carbon dioxide from the lungs.

ACIDOSIS	PH	BLOOD		URINE	REACTION
		CO ₂	Cl		
RESPIRATORY ACIDOSIS					
CAUSE					
1. RETENTION OF CO ₂	LOW	ELEVATED OR NORMAL	LOW OR NORMAL	NORMAL	ACID OR ALKALINE
A. PULMONARY DISEASE					
B. HEART DISEASE					
C. HYPOPNEA (CENTRAL)					
METABOLIC ACIDOSIS					
CAUSES					
1. EXCESSIVE PRODUCTION OF ORGANIC ACIDS	NORMAL OR LOW	LOW	NORMAL OR LOW	NORMAL	ACID
A. DIABETES MELLITUS					
B. STARVATION					
C. GLYCOGEN STORAGE DISEASE					
2. ACID RETENTION	NORMAL OR LOW	LOW	NORMAL OR LOW	NORMAL	ACID
A. RENAL DISEASE					
B. DEHYDRATION					
3. INGESTION OF MINERAL ACIDS OR ACID PRODUCING SALTS	NORMAL	LOW	INCREASED	NORMAL	ACID
IN CaCl ₂ OR NH ₄ Cl					
4. EXCESSIVE LOSS OF BASE	NORMAL OR LOW	LOW	LOW	LOW	ACID
A. DIARRHEA					
B. ADDISON'S DISEASE					
ALKALOSIS					
RESPIRATORY ALKALOSIS					
CAUSE					
1. HYPERVENTILATION	ELEVATED	LOW OR NORMAL	NORMAL	NORMAL	ALKALINE OR ACID
A. SALICYLATE INTOXICATION					
B. MENINGITIS OR ENCEPHALITIS					
C. HIGH ALTITUDES					
METABOLIC ALKALOSIS					
CAUSES					
1. LOSS OF HCl VOMITING	NORMAL OR ELEVATED	ELEVATED	LOW	NORMAL	ALKALINE
2. INGESTION OF ALKALI	NORMAL	ELEVATED	NORMAL	INCREASED	ALKALINE

Chart 2.

With obstruction to the escape of carbon dioxide from the alveoli or from other causes listed heretofore, there is an increase of carbon dioxide in the blood. Of the two forms in which carbon dioxide occurs in the blood, the $B.HCO_3$, which is dependent on residual base and renal control is the more fixed, and so the increase is relatively greater, at least at first, in the $H.HCO_3$ fraction, with a disturbance in the 1:20 ratio. As pH is equal to 6.1 plus $\log \frac{B.HCO_3}{H.HCO_3}$, the increase in $H.HCO_3$ causes a reduction in pH and an uncompensated acidosis. To compensate, there needs to occur an increase in $B.HCO_3$, which could be made possible by renal reduction of chloride, permitting accumulation of $B.HCO_3$ and return of the carbon-dioxide-bicarbonate buffer

system toward the normal ratio of 1:20. In some cases return is incomplete and the plasma pH may remain low, especially if fluid intake is poor and renal excretion is impaired. It is of interest to note that if in compensated respiratory acidosis the cause of the condition leading to the increase of carbon dioxide in alveolar air should be removed suddenly, the carbon dioxide may escape rapidly, leaving an excess in the blood of uncompensated B.HCO_3 . The patient would then quickly present a picture of alkalosis and even tetany. This train of events has been observed after tracheotomy in patients with laryngeal obstruction.

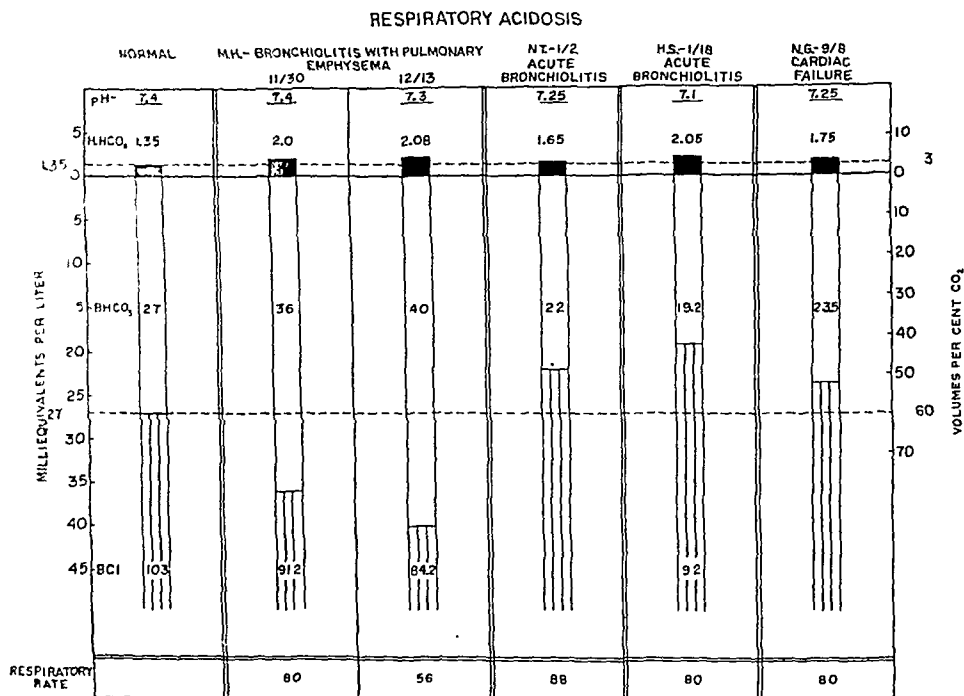


Chart 3.

The demonstration of acidosis when the respiratory mechanism is responsible requires the determination of total carbon-dioxide content of the blood plasma which measures carbon dioxide both as H_2CO_3 and B.HCO_3 and the measurement of plasma pH. The greatest change in the total carbon-dioxide content may not be in the H_2CO_3 but rather the B.HCO_3 . The symptoms of acidosis in a patient with a total plasma bicarbonate as high as 88 to 99 volumes per cent become explainable when measurement of pH is made in addition to total bicarbonate determinations. Much clearer definition of the problem would be achieved with H_2CO_3 and B.HCO_3 measured separately. However, from measurement of pH and total bicarbonate the ratio of H.HCO_3 - B.HCO_3 can be computed.

Two further findings in patients with respiratory acidosis merit consideration. One is the low plasma chloride noted in some of these patients. The

reduction in blood chloride is probably due to a renal compensatory adjustment to the accumulation of carbonic acid in the blood plasma; thus, when an excess of H.HCO_3 accumulates in the plasma, chloride excretion through the kidneys would leave more base available to permit an increase in B.HCO_3 and return $\frac{\text{H.HCO}_3}{\text{B.HCO}_3}$ toward the 1:20 ratio. That this is the mechanism permitting increase in B.HCO_3 rather than through extension of total base has been demonstrated by a number of investigators²⁻⁴ and was observed in one of our patients (Chart 3). The urine at first should then be acid. Davies and associates⁵ showed that in acute cases of respiratory acidosis there was diuresis, with doubling of ammonia excretion and increased acidity of the urine. The chloride excretion was not measured. It would seem, however, that to facilitate renal compensation of respiratory acidosis, fluids such as saline or Ringer's solution with their high chloride content are contraindicated, as they would interfere with the attempt of the kidney to lower plasma chloride and thereby permit increase of B.HCO_3 .

The second finding that deserves explanation, especially in view of the necessity for increased chloride excretion, is the presence of alkaline urine in one of our patients, M. H. In that patient, however, the B.HCO_3 had increased to 80 plus volumes per cent and had largely compensated for the H.HCO_3 increase as evidenced by pH of 7.3. It would then seem that no longer needing to accomplish the preferential excretion of chloride, the kidneys had begun to share the respiratory responsibilities of ridding the body of excess carbon dioxide in the form of HCO_3^- . It is unfortunate that the source of the covering base was not measured. However, that the kidneys can be but slightly effective in taking over the respiratory function of removing carbon dioxide becomes apparent when it is recalled that in the adult as much as two pounds of carbon dioxide may demand excretion through the lungs in twenty-four hours.

Thus, it can be seen how misunderstanding of respiratory acidosis and alkalosis may arise when pH determinations of the plasma are not made and the condition is judged by the reaction of urine or by carbon-dioxide content of the blood plasma. The retention of carbonic acid may truly upset normal mechanisms and result in extension of carbonic acid and bicarbonate in the plasma, but with the appearance in the patient of signs of acidosis. The extension of bicarbonate occurs in order that the 1:20 ratio of the carbon-dioxide-bicarbonate buffer system may be maintained, but in many cases there is enough failure of this mechanism to permit a persistently low pH. The increase in bicarbonate covering base may not occur, and when it does not, there is less compensation and still lower plasma pH. This is illustrated in patients H. S. and N. T. in contradistinction to patient M. H. (Chart 3).

CASE REPORTS OF RESPIRATORY ACIDOSIS IN INFANCY

M. H., a 3-week-old infant, was admitted to the Babies and Childrens Hospital of Cleveland on Nov. 24, 1945, with a chief complaint of rapid labored breathing. Following birth, no respiratory embarrassment was observed for the first forty-eight hours. On the third day of life the patient's respirations became labored. The rate became rapid, and difficult expirations and expiratory wheezes were noted. Occasionally large amounts of

mucus collected in the nasopharynx. On admission, the respiratory rate was 36 per minute but later varied between 50 and 80 per minute. There was generalized cyanosis, the chest was markedly increased in anterior-posterior diameter and was hyperresonant to percussion. Supraclavicular and substernal retraction occurred during inspiration. Fine crepitant and sonorous râles were heard throughout the chest with the greatest intensity at the bases. The heart and spleen were on the right, the liver on the left.

The white blood cell count was 26,000 at the time of admission, dropping gradually in the next few days to 11,500. The red blood cells numbered 5.5 million and the hemoglobin was 61 per cent. The urine was acid in reaction. Five days after admission, on Nov. 29, 1945, the plasma pH was 7.3 with a total carbon-dioxide content of 98.9 volumes per cent. During the early hospital days the plasma pH remained at 7.3 with the total carbon dioxide content varying between 83 and 99 volumes per cent. The plasma H_2CO_3 , therefore, ranged between 4.2 and 5.7 volumes per cent and the carbon-dioxide tension between 66-99 mm., an increase which at its height was almost twice normal. The plasma chlorides were lowered to around 300 mg. per cent (85 meq. per liter). Roentgenograms of the chest showed an area of consolidation in the medial portion of the right apex. A shadow, thought to be caused by atelectasis, protruded from the left hilus and extended almost to the axillary line. The most striking feature, however, was the bilateral increased radiability of the peripheral lung fields.

A diagnosis of diffuse bronchiolitis with secondary emphysema was made. The clinical findings together with the elevated plasma carbon dioxide, lowered pH, and reduced chlorides led to a secondary diagnosis of partially compensated respiratory acidosis. The acute symptoms seemed unrelated to the situs inversus of the major organs. The infant was treated with steam inhalation, aspiration of the pharynx, and administration of expectorants as well as of penicillin in usual dosages. Improvement was gradual but recovery from the acute process was never complete.

In the previous patient, our first chemical studies were not done until the eighteenth day of her illness. Subsequently, we set out to determine whether, early in bronchiolitis, despite increased rate and depth of respirations, there was enough elevation of plasma H_2CO_3 due to decreased ventilation to make respiratory acidosis an important factor in that disease. Chemical measurement of plasma pH and total carbon-dioxide content was obtained in twenty-one infants presenting the clinical picture of bronchiolitis. In two of these patients, early in the disease, there was evidence of elevation in the plasma H_2CO_3 with resultant respiratory acidosis.

N. T., a 5-week-old white boy, was admitted on Jan. 2, 1947, with a history of illness of one day's duration. He was a poorly nourished infant appearing acutely and critically ill. He was comatose and exhibited an ashen gray pallor; temperature was 37.4°C , pulse 140, and respirations were 80 and shallow. The expansion of the chest was equal, percussion was resonant, but on auscultation there were many fine and coarse râles heard in both lung fields. Streaked densities in the right upper lung field and in the region of the right cardiophrenic angle were observed in the x-rays of the chest. The left lung appeared clear. The plasma pH was found to be 7.25 and the carbon-dioxide content 52.9 volumes per cent or 23.8 meq. per liter, indicating a plasma H_2CO_3 of 3.6 volumes per cent or 1.6 meq. per liter and carbon-dioxide tension of 55 mm. Despite the use of expectorants and chemotherapy and other efforts to relieve bronchiolar obstruction, the respirations remained rapid, between 80 and 100. On the fourth hospital day, the child suddenly had a massive hemorrhage from a duodenal ulcer which proved to be fatal. The presence of the ulcer was deemed unrelated to the acute pulmonary disease.

H. S., aged 20 months, was admitted to the hospital Jan. 19, 1947, with a history of having had frequent attacks of asthmatic bronchitis or bronchiolitis since the age of 15 months. It had been noted two days before entry that the patient was breathing rapidly.

On admission the child appeared acutely and seriously ill. The temperature was 40.4°C ., pulse 140, and respirations were 88. Expiration was prolonged but there were no wheezes. There was slight cyanosis. The chest was distended and the A-P diameter seemed increased. There was slight dullness to percussion over the right lower lobe. Crepitant râles were heard in the right chest posteriorly and rhonchi were present throughout the chest. The urine was found to be acid in reaction. The white blood cell count was 17,500, of which 72 per cent were polymorphonuclear leucocytes. The plasma pH was 7.1; the total plasma carbon-dioxide content 47.5 volumes per cent or 21.3 meq. per liter, and the plasma H.HCO_3 , determined on the basis of the foregoing, was 4.5 volumes per cent or 2.0 meq. per liter, and the carbon-dioxide tension 67 mm. The chlorides were 92 meq. per liter. Steam and hydriodic acid were instituted in an effort to relieve the bronchial obstruction and chemotherapy to combat the infection. On the second day respirations were slightly less rapid, 60 per minute, but were still labored. The urine was scant, acid in reaction, and contained \pm plus albumin. The plasma pH was 7.28; carbon-dioxide content 35.5 volumes per cent or 15.9 meq. per liter; H.HCO_3 , 2.1 volumes per cent or 0.97 meq. per liter; carbon-dioxide tension 32 mm. and chlorides 106 meq. per liter. Despite all therapy, temperature rose to 42.5°C . that day and the child expired.

In this infant, during his first day of hospitalization, there was enough elevation of plasma H.HCO_3 in the presence of a relatively normal B.HCO_3 to produce a plasma pH of 7.1. These chemical changes plus the pulmonary findings presented the picture of an uncompensated respiratory acidosis. On the second day the situation changed. Apparently there had occurred enough decrease in the bronchial obstruction to allow the plasma H.HCO_3 to fall from 4.5 volumes per cent to 2.1 volumes per cent. However, during the same period the plasma CO_2 content also fell so that despite the decrease in plasma H.HCO_3 , an uncompensated acidosis, although less severe than the first day, still persisted, with a lowering of the pH to 7.28. The oliguria and marked albuminuria suggest that the decrease in plasma carbon-dioxide content might have been secondary to renal dysfunction and that a renal acidosis had occurred terminally.

The chemical findings in these patients are pictured in Chart 3.

While cyanosis characterizes inadequate oxygen exchange in lungs, rapid labored respiration should call attention to the possibility of carbon-dioxide elevation due to limitation of ventilation capacity. Davies and co-workers⁵ in cases of respiratory acidosis in adults, observed respiratory volumes as great as 30 L. per minute. In our cases, obstruction of bronchioles seemed to be the common cause of respiratory acidosis, an obstruction which usually was so far down the bronchial tree and so in the periphery of the lung fields that aspiration from above would fail to relieve the condition. Our patients have been acutely ill with fever, rapid respirations, distended, barrel-shaped, emphysematous chests, and with numerous râles throughout the lung fields. Oxygen has failed to relieve the embarrassment, although it may improve the patient's color. It has been suggested that oxygen administration, by increasing the viscosity of the bronchial secretions, may actually increase the bronchiolar obstruction.⁶ Atropine and codeine on the same basis should probably be avoided. Bronchial dilator drugs as ephedrine together with the use of expectorants such as hydriodic acid and steam inhalation would appear indicated. The increased humidity has seemed to be most helpful in decreasing the

viscosity of the bronchial mucus and relieving the obstruction. Chemotherapy has been only occasionally effective. If the deep pulmonary obstruction is relieved, the acid-base relationship promptly returns to normal and the child's respirations, which have been rapid, labored, and deep and have failed to respond to oxygen inhalation, return to a normal level.

Just as instances of respiratory acidosis have been recognized, so have cases presenting the picture of respiratory alkalosis.

MECHANISM OF RESPIRATORY ALKALOSIS

The mechanism responsible for the development of respiratory alkalosis is hyperventilation with an increase in rate and depth of respiration. In patients with salicylate intoxication, with meningitis or encephalitis, or with hyperpyrexia, hyperventilation seems dependent on disturbance of the respiratory center. In a rapid ascent to high altitudes, respiratory alkalosis may result from the difference between intrapulmonary and atmospheric carbon-dioxide pressures. In both instances, hyperventilation induces loss of carbon dioxide, first from the alveoli of the lungs and then from the blood.

As in respiratory acidosis, there is a derangement of the $\text{H.HCO}_3\text{-B.HCO}_3$ ratio in the plasma. With loss of CO_2 from the lungs there is a diminution in the free carbonic acid of plasma which, unless compensated by a decrease of B.HCO_3 results in a decrease in ratio of 1:20 and an increase in pH and an uncompensated alkalosis.

To compensate for the uncontrolled loss of carbon dioxide through the lungs, there needs to be a decrease in B.HCO_3 . This could occur through elevation of chloride ion which would decrease the residual base available for combination with HCO_3^- and, therefore, the B.HCO_3 . That an increase in chloride ion does occur in respiratory alkalosis has been pointed out by Peters and Van Slyke,⁷ Gamble,² and Guest and co-workers.⁸ Some investigators have further noted that in patients with respiratory alkalosis there also occurs an increase in plasma lactic acid and ketone bodies by a mechanism not understood.⁹ Such a change could also aid in the decrease of the B.HCO_3 and the return of the plasma pH toward normal.

The task of compensation, with the respiratory system deranged, rests largely on the renal mechanism. As the kidney attempts to maintain the osmotic pressure and the total base at a constant level in the blood, to lower the B.HCO_3 to balance the fall in H.HCO_3 , it would have to retain chloride or other anions. This could be accomplished by preferential excretion of HCO_3^- over Cl^- with the production of an alkaline urine. Actually, as reported by Collip¹⁰ and Davies,⁵ this tends to occur to some degree after forced hyperventilation before the adjustment of chlorides gets under way. However, over a prolonged period, such a way to reduce B.HCO_3 might be poor physiologically because it involves a progressive loss of base. In our patients the urine continued to be acid in reaction despite plasma pH levels between 7.5 and 7.8. This may have been a factor in the maintenance of an uncompensated decrease in H.HCO_3 with persistently elevated pH and uncompensated alkalosis.

With the respiratory mechanism deranged and with the renal mechanism unable to cope rapidly with the situation, it would seem that the correction of respiratory alkalosis should be sought by correction of the cause of the hyperventilation. However, to help renal efforts to restore acid-base balance, the administration of chloride would appear indicated. In cases of respiratory alkalosis due to respiratory center dysfunction, administration of drugs such as morphine to inhibit the respiratory center may prove effective. It appeared to be of benefit in our first patient, B. T. In dogs, Rapaport and Guest¹¹ found barbiturates more effective than morphine in controlling the hyperventilation secondary to salicylate intoxication. In respiratory alkalosis due to ascent to high altitudes, pressurized breathing equipment will usually restore normal relationship.

The diagnosis of respiratory alkalosis as of respiratory acidosis is dependent on estimation of both the total plasma carbon-dioxide content and plasma pH. The chemical findings in respiratory alkalosis are those of normal or decreased carbon-dioxide content and elevated pH. This is in contrast to findings in metabolic alkalosis such as follows vomiting where there is an increase in total carbon-dioxide content and normal or elevated pH.

CASE REPORTS OF RESPIRATORY ALKALOSIS IN CHILDREN

B. T., a 9-year-old white boy, was admitted to the private service of Babies and Childrens Hospital on May 26, 1946, with a history of migratory joint pains and fever of five days' duration. On admission the temperature was 39.2° C., pulse 80, respirations 24, blood pressure 96/50. Abnormal physical findings were limited to the heart and extremities. The heart did not appear to be enlarged; sounds were of good quality and normal except for a blowing systolic murmur which was heard over the apex and was transmitted to the axilla. Pain was elicited on palpation of the left knee. There was no redness or swelling of any of the joints. Blood examination showed a red blood cell count of 4.0 million with 75 per cent hemoglobin and a white blood cell count of 7.9 thousand, of which 88 per cent were polymorphonuclear leucocytes. Sedimentation rate by the Westergren method was 72 mm. in one hour (normal under 10). The urine was normal. At 8 P.M., the day of admission, the attending physician started the patient on an infusion of 1,000 c.c. of normal saline containing 10 Gm. sodium salicylate. Six hours after the start of the infusion, the child had received 900 c.c. and approximately 9 Gm. sodium salicylate. At that time it was noted that the respirations were deep; the child was extremely restless, complained of excessive thirst, and had two episodes of emesis. The infusion was immediately stopped. Through the remainder of the night the child remained restless and disoriented and kept visualizing objects such as snakes and monkeys. The respirations remained about 28 per minute but were increased in depth. On chemical examination of the blood the next morning, the plasma pH was found to be 7.6 and the total carbon-dioxide content was 35.7 volumes per cent or 16.1 meq. per liter, indicating that the plasma H_2HCO_3 was lowered to 1.1 volumes per cent or 0.51 meq. per liter and that the carbon-dioxide tension was 16 mm. The nonprotein nitrogen was 27.5 mg. per cent and the blood salicylate level was 810 μg per cubic centimeter. The urine showed a specific gravity of 1.006, acid reaction, and no albumin, sugar, or acetone. Intravenous administration of lactate Ringer's solution was started and attempts were made to increase the plasma H_2HCO_3 by having the patient rebreathe his expired air and later having him breathe a mixture of 95 per cent oxygen and 5 per cent carbon dioxide. The child resisted both procedures and during that day had several short generalized convulsions. Sodium phenobarbital, one grain intramuscularly, was also tried but had no effect on either rate or depth of respiration. At 5:30 P.M. the plasma pH was 7.6 and the carbon-dioxide content was 40.4 volumes per cent or 19.7 meq. per liter. Fluids were forced by mouth and

an infusion of 500 c.c. of 5 per cent glucose in water was started. By midnight the child had received a total of 2,640 c.c., of which 700 c.c. had been administered intravenously, and had excreted 640 c.c. of urine. The urine was consistently acid. By midnight the respirations had increased in rate to 32 per minute and were still deep. The child at that time was given morphine sulfate, $\frac{1}{6}$ grain subcutaneously. An hour later the patient seemed much more comfortable, respirations had become slower, falling to 24 per minute, and were less deep. The child was still slightly disoriented. By noon of May 28, the child had received another 1,290 c.c. of fluid orally and had excreted 300 c.c. of urine which was again acid in reaction. Chemical measurements of the blood then showed the pH still to be 7.6, carbon-dioxide content was 56.8 volumes per cent, or 25.5 meq. per liter; chloride was 92 meq. per liter; sodium 140 meq. per liter and salicylate level was 331 μ g per cubic centimeter. Sedimentation rate at this time done by the Westergren method showed a fall of 84 mm. in one hour. At 4:30 P.M. the child was much improved. The plasma pH had fallen to 7.55 and the carbon-dioxide content was 59.3 volumes per cent or 26.7 meq. per liter. The urine remained acid in reaction. On May 29, the child appeared to be well oriented, his respiratory rate was 24 per minute but breathing was still deeper than normal. The child's general reaction seemed normal except that he was drowsy. The plasma pH was 7.55 and the carbon-dioxide content was 59.6 volumes per cent or 26.9 meq. per liter. The chloride was 92 meq. per liter; sodium was 141 meq. per liter and the salicylate blood level was 140 μ g cubic centimeter. Urine was acid. On May 30, respirations dropped to 20 per minute and subsequently remained normal both in depth and rate. May 31, the plasma pH had fallen to 7.46; the carbon-dioxide content was 62.5 volumes per cent or 28.1 meq. per liter. Five days later the patient was restarted on sodium salicylate, one gram by mouth every eight hours. The child remained on this dosage without any ill effects for approximately one month, during which time the sedimentation rate slowly fell to normal. On June 24, sedimentation rate was 9 mm. in one hour by the Westergren method (Chart 4).

C. N., a 7-year-old white girl, was admitted to the hospital on Nov. 15, 1946, with a history of having had some vague pains in the extremities since the preceding spring. Three days before admission she had complained of precordial pain and had been noted to have dyspnea, malaise, and fever. On admission she appeared well developed, slightly undernourished, but not acutely ill. Temperature was 37.7° C.; pulse 110; respirations 34; blood pressure 100/70. Weight was 20.9 kg. On physical examination the heart did not appear to be enlarged. Rhythm was regular but there was a moderately loud, harsh systolic murmur heard best at the apex and slightly transmitted to the axilla. The urine was normal. The red blood cell count was 4.35 million with 9.5 Gm. of hemoglobin. The white blood cell count was 7.15 thousand, of which 59 per cent were polymorphonuclear leucocytes. The sedimentation rate was 65 mm. in one hour by the Westergren method.

During the first hospital day the patient received by mouth a total of 5 Gm. of sodium salicylate. At the end of that time she vomited, complained of tinnitus, and the respirations, although remaining at the rate of 34 per minute, were increased in depth. Nov. 17, 1946, the blood pH was 7.48 and the carbon-dioxide content was 47.7 volumes per cent or 17 meq. per liter and the blood salicylate level was 400 μ g per cubic centimeter. During that night the child continued to have some emesis and an infusion of 1,500 c.c. of glucose in saline was started. The morning of Nov. 18 the child appeared lethargic, the respirations had increased in rate to 48 per minute and were still labored. The child, however, remained well oriented and had no convulsive movements. At this time the pH of the plasma had risen to 7.50 and the carbon-dioxide content was 46.4 volumes per cent; the salicylate level was 260 μ g per cubic centimeter. The urine was acid with a pH of 5.5. Respirations remained between 30 and 40 on November 19 and 20, but fell to 22 on November 21 (Chart 5).

A. K., an 11-year-old white girl, was admitted to the hospital on July 26, 1946, with a history of having had migratory joint pains and fever of five weeks' duration together with evidence by examination of mitral valve involvement. She had had one episode of migratory arthritis two years before admission, at which time there had been no evidence of cardiac disease. On admission the temperature was 38.1° C.; pulse 128; respirations 24; blood pressure 126/46. Weight was 37.1 kg. The child appeared apprehensive and chronically ill.

BT. - AGE 9 YRS. (ACUTE RHEUMATIC FEVER)

		5/26	5/27		5/28		5/29	5/30	5/31
			A.M.	P.M.	A.M.	P.M.			
SYMPTOMS:									
	HYPERPNEA	-	++++	++++	++	+	+	-	-
	RATE OF RESP.	24	28	32	26-18	24	24	20	20
	CONVULSIONS	-	+	+	-	-	-	-	-
	DELIRIUM	-	++	+	-	-	-	-	-
	TINNITUS	-			+	+	-	-	-
BLOOD:									
	pH		7.6	7.6	7.6	7.55	7.55		7.47
	CO ₂ VOL%		35.7	40.4	56.8	59.3	59.6		62.5
	Cl meq/L.				92		92		
	Na meq/L.				140		141		
URINE:									
	REACTION		ACID	ACID	ACID	ACID	ACID		
	ACETONE		-	-	-	-	-		
SALICYLATE:									
	BLOOD LEVEL %/CC.		810		331		140		0
	DOSAGE IV.	9 GM.	-	-	-	-	-	-	-

Chart 4.

CN - AGE 7 YRS. (ACUTE RHEUMATIC FEVER)

	11/16	11/17	11/18	11/19	11/20	11/21
RESPIRATIONS:						
RATE	34	34	48	40-30	40-30	22
DEPTH	-	+++	+++	++	++	-
BLOOD:						
pH		7.48	7.50			
CO ₂ VOL.%		37.7	46.4			
URINE:						
pH			5.5			
SALICYLATE:						
BLOOD LEVEL r/cc.		400	260			
DOSAGE (ORAL)	5 Gm.	-	-	-	-	-

Chart 5.

Abnormal physical findings were limited to the heart. There was a marked increase in precordial activity. The heart was slightly enlarged to the left, rhythm was regular, sounds were of fair quality. At the apex, both sounds were replaced by a low rumbling systolic murmur and a soft blowing diastolic murmur which continued until systole. Pulmonic second sound seemed to be slightly accentuated. By x-ray the heart was enlarged; the right border of the cardiac silhouette appeared normal, the left border was unusually rounded in its upper half so that instead of presenting a concavity in the region of the pulmonary arch there was a convexity. The electrocardiogram was within normal limits. The red blood cell count was 3.62 million with 63 per cent hemoglobin. The white blood cell count was 8.6 thousand of which 68 per cent were polymorphonuclear leucocytes. The urine was normal. The nonprotein nitrogen was 22.3 mg per cent and carbon dioxide content was 50.3 volumes per cent or 22.6 meq per liter. The sedimentation rate by the Westergren method showed a fall of 75 mm in the first hour. The child was started on sodium salicylate, one gram, and sodium bicarbonate, one gram, to be given five times a day. Four days after entry, July 30, the child had some nausea and emesis and the sodium bicarbonate was discontinued. It was then first noted that the respirations were slightly more rapid than on admission and increased in depth. The rate varied between 30 and 32 per minute. On August 1 the blood salicylate level was 695 μ g per cubic centimeter. On August 2 the rate and depth of respiration were further increased, the rate varying between 36 and 40. At that time chemical examination of the blood revealed the total plasma carbon dioxide content to be 37.3 volumes per cent or 17 meq per liter, the pH to be 7.55, the salicylate level was 545 μ g per cubic centimeter. Salicylates were discontinued for a period of forty eight hours. On August 4, the respirations had decreased in rate to 24. Salicylates were again started in a dosage of one gram four times daily and in two days the respiratory rate again showed an elevation, this time to 40 per minute with a marked increase in the depth of the excursions. On August 6 the plasma carbon dioxide content was 32.2 volumes per cent and the pH was 7.6. The salicylate level was 276 μ g per cubic centimeter. Salicylates were again discontinued and on August 7, although the respiratory rate seemed unchanged, the depth of the excursions was less marked. Total plasma carbon dioxide content was then 55.6 volumes per cent or 25 meq per liter; the pH had dropped to 7.4 and the blood salicylate level was 60 μ g per cubic centimeter. August 8, the rate and depth of respirations had returned to normal. The total plasma carbon dioxide content was 47.3 volumes per cent and pH 7.4. Urine during this period was consistently acid in reaction. There were no convulsions or disorientation (Chart 6).

M. A. V., a 9 year old white girl, was admitted to the hospital Sept. 17, 1946 for treatment of acute rheumatic fever and rheumatic heart disease. During the hospital admission, while the child was receiving sodium salicylate, 0.64 Gm. every six hours, it was noted that the respiratory rate increased from a level of 20-28 to 50, and that the depth increased markedly. With the increase in rate and depth of respirations there were no untoward symptoms such as disorientation, emesis or tinnitus. Chemical examination of the blood, however, showed a salicylate level of 308 μ g per cubic centimeter, a total plasma carbon dioxide content of 52.8 volumes per cent or 23.7 meq per liter, and a pH of 7.62. The urine pH was 7.2. The salicylates were discontinued and it was seventy two hours before the respirations returned to normal, subsequently, the child was restarted on sodium salicylate 0.32 Gm. four times daily. With this, there was no alteration in respirations and a check of the blood revealed the pH to be 7.49 with a total carbon dioxide content of 59.7 volumes per cent or 26.9 meq per liter.

The course in the foregoing patients has been described in some detail, since the wave of enthusiasm for massive salicylate therapy portends an increase in the number of cases of respiratory alkalosis that may be observed subsequent to salicylate poisoning. The mechanism whereby salicylates produce hyperventilation appears to be by direct stimulation of the respiratory center.¹¹ It is to be noted that in the milder cases an increase in blood pH occurred shortly

after the administration of salicylates had induced increased rate and depth of breathing. Not all patients developed tinnitus and emesis, but the more severe cases did show such symptoms and in one patient tetany and convulsions ensued. Furthermore, a considerable period was required to clear the blood of salicylates after the administration of the drug had been stopped, and until such time the respirations remained deep and the pH of the blood elevated. None of these patients with salicylate poisoning showed evidence of acidosis.

A.K. - AGE 11 YRS. (ACUTE RHEUMATIC FEVER)

	7/26	7/27 → 8/1	8/2	8/4 → 8/5	8/6	8/7	8/8
RESPIRATIONS:							
RATE	24	24-30	36	24-30	40	40	26
DEPTH	-	- +	+++	+	+++	+	-
BLOOD:							
pH			7.55		7.6	7.4	7.4
CO ₂ VOL. %	50.3		37.3		32.2	55.6	47.3
URINE:							
REACTION			ACID			ACID	ACID
SALICYLATE:							
BLOOD LEVEL μ /CC.			545		276	60	
DOSAGE (ORAL)	5 GM. DAILY		-	4 GM. DAILY		-	-

Chart 6.

The question has arisen as to why sodium bicarbonate was not administered to some of our patients in an effort to increase the salicylate excretion. Theoretical considerations lead one to presume that use of sodium bicarbonate may render more marked the alkalosis, thus increasing the tendency to tetany and convulsions, while experience in one case showed definitely that use of sodium bicarbonate in conjunction with the sodium salicylate did not prevent the appearance of respiratory alkalosis. To permit physiologic compensation to excess carbon-dioxide loss, chloride administration would appear indicated.

C. K., aged 3 years, was admitted to the hospital on Dec. 20, 1946, with signs of meningitis of probably two weeks' duration and coma and convulsions of one week's duration. Temperature was 40.5° C.; pulse 120; respirations 64 per minute.

She was a well developed, well-nourished white girl, spastic, comatose, and breathing deeply and rapidly. Spinal fluid was under increased pressure, was turbid, and contained 13,750 polymorphonuclear leucocytes per cubic millimeter; no sugar was found and many gram negative bacilli were seen in direct smear which proved to be type B. *H. influenza*. Chemical examination on admission showed the plasma pH to be 7.8 and the total carbon-dioxide content 51 volumes per cent or 22.7 meq. per liter, indicating a decrease in plasma H_2HCO_3 to 1.0 volume per cent or 0.45 meq. per liter and carbon-dioxide tension of 15 mm. Urine was neutral in reaction.

Specific therapy was instituted immediately and on Dec. 31, 1946, although the child continued to be comatose, there was a decrease in temperature and a decrease in the rate and depth of respirations. The plasma pH was found to be 7.72; carbon dioxide content 54 volumes per cent; chloride 96 meq per liter and sodium 138 meq per liter. On January 2, the rate of respirations had fallen to 30 per minute but the depth was still increased. Chemical examination of the blood on that date showed a fall in plasma pH to 7.65. The total plasma carbon dioxide content was 53.3 volumes per cent or 23.9 meq per liter. Chloride was 100 meq per liter and sodium was 142 meq per liter. The urine was acid in reaction. The respirations did not return to normal depth and rate and the child subsequently succumbed to the *H. influenza* infection, however, a check of the blood analysis on January 21, when respirations were relatively normal in depth, showed the plasma pH to be 7.5, the total plasma carbon dioxide content 53 volumes per cent and plasma H HCO_3 of 2 volumes per cent (Chart 7). In this patient, where there was little decrease in B HCO_3 from normal, there was less compensation and a greater change in pH than was observed in our other cases of respiratory alkalosis (Charts 4 to 6).

C.K.- AGE 3 YRS. (H. INFLUENZAL MENINGITIS)

		12/30	12/31	1/1	1/2
RESPIRATIONS:					
	RATE	64	60-30	52-28	40-24
	DEPTH	++++	+++	+++	++
BLOOD:					
	pH	7.8	7.72		7.65
	CO_2 VOL. %	51	54		53.3
	Cl m eq/L.		96		100
	Na m eq/L.		138		142
URINE:					
	REACTION	NEUTRAL			ACID

Chart 7

The observations in this patient suggest that spasticity and convulsions associated with meningitis may in some instances be due to alkalosis, secondary to hyperventilation due in turn to derangement of the respiratory center.

M. V., a 1 month old white girl, was admitted on Aug. 5, 1947, with a chief complaint of rapid, labored respirations since 6 weeks of age. The infant had been born at term by a normal spontaneous delivery with no difficulty in resuscitation. However, during the first three months of life, she had vomited one to three times a day, the vomitus containing only food of the previous meal, no bile or blood. Since the onset of rapid respirations there had been occasional cough but no fever.

She was a poorly developed, white female infant breathing rapidly (64 per minute) with an expiratory grunt and moderate retraction of the lower ribs and sternum on inspiration. The skin was ashen pale; there was no cyanosis. The chest was resonant to percussion. On auscultation many coarse and fine rales were heard throughout both lung fields, more marked at the bases. Remainder of examination was negative.

The red blood cell count was 4 million with 79 per cent hemoglobin. The white blood cell count was 4.6 thousand c.mm., of which 20 per cent were polymorphonuclear leucocytes, 12 per cent eosinophiles, 64 per cent lymphocytes, and 4 per cent monocytes. Sedimentation rate was 9 mm. in one hour. Sputum examination revealed no eosinophiles and a culture showed alpha hemolytic streptococcus and *Staphylococcus aureus*. Tuberculin 1:1,000 was negative. Absorptive studies with fat, protein, and glucose were normal. Blood Wassermann was negative. Urine was normal and acid in reaction.

X-rays of the chest showed the cardiac size and contour to be normal. There was moderate streaking along the bronchovascular markings adjacent to the heart bilaterally.

It was our impression that the infant had a chronic pneumonitis possibly secondary to aspiration of foreign material. Inhalation by nebulization every three hours of a mixture of neosynephrin and penicillin with carbogen was followed by postural drainage. Respirations remained 60 per minute, unchanged in character, and the pulmonary findings persisted. On the fifth hospital day, Aug. 11, 1947, plasma pH was 7.6 and total carbon-dioxide content was 61.8 volumes per cent indicating a decrease in plasma H_2CO_3 to 1.9 volumes per cent and carbon-dioxide tension to 29 mm. On August 13 the plasma pH was still 7.6 and the total carbon-dioxide content was 63 volumes per cent. Chlorides were 86 meq. per liter.

Why the chlorides were low despite absence of vomiting for over a month is not clear. Yet, that the lowering of the chlorides was not the cause of the alkalosis would seem likely when we note that the total carbon-dioxide content was relatively normal and that the greatest alteration was in the H_2CO_3 . This last finding plus the rapid respirations would indicate a respiratory cause for the alkalosis. The child was given ammonium chloride, 0.5 Gm. every four hours. At the end of four days, despite no change in rate or character of respirations, plasma pH was 7.45, total carbon-dioxide content was 44.6 volumes per cent, and chlorides were 100.5 meq. per liter. This compensation occurred without any change in the H_2CO_3 , which remained at 1.9 volumes per cent.

The cause for the respiratory alkalosis in this patient was possibly anoxia. As carbon dioxide is more diffusible than oxygen, the increased ventilation necessary to maintain adequate oxygenation in such a patient might be associated with increased alveolar carbon-dioxide loss. This in turn would produce a lowering of the plasma H_2CO_3 and a possible respiratory alkalosis. That such a course of events follows anoxia has been reported by a number of investigators.^{9, 12-14} Also, in the previously mentioned observations in twenty-one infants with acute pulmonary infection with rapid and labored respirations, six showed a plasma pH between 7.5 and 7.6 with total carbon-dioxide contents which were either normal or low.

The aforementioned case further amplifies the importance of chlorides in obtaining compensation in instances of respiratory alkalosis. However, just as in the instances of respiratory alkalosis due to hyperventilation secondary to central stimulation, actual recovery is dependent on elimination of the cause of increased ventilation which in the above patients was the pulmonary infection.

Chart 8 graphically depicts the chemical findings in some of our patients with respiratory alkalosis.

SUMMARY

Respiratory acidosis and alkalosis occur probably more frequently than is generally believed and should be considered in patients presenting derangements of the respiratory mechanism. Cases illustrating the two conditions are presented.

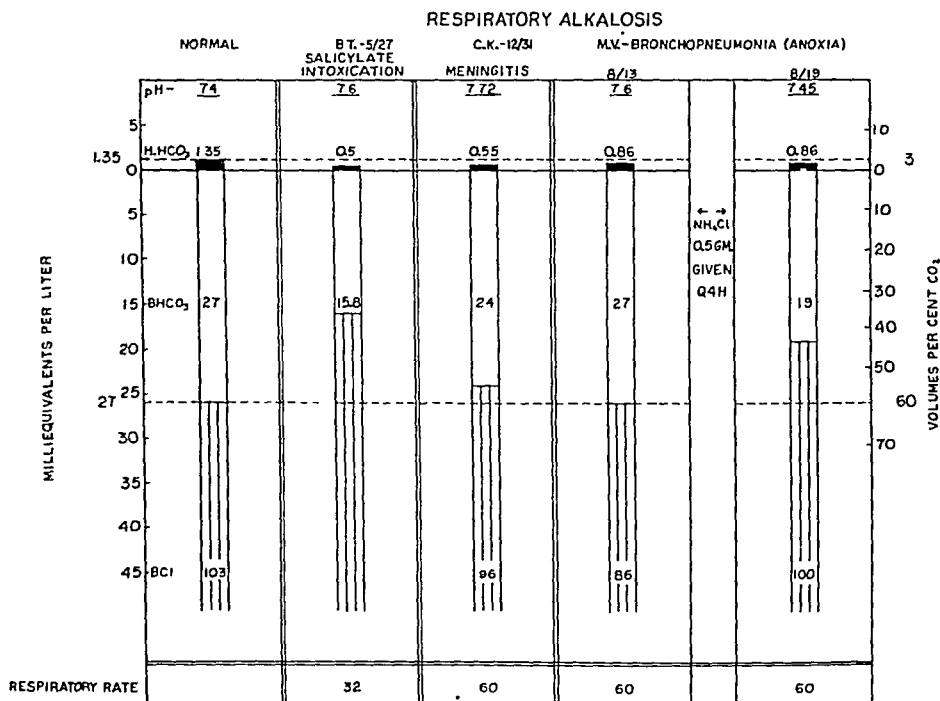


TABLE I

RESPIRATORY ACIDOSIS	RESPIRATORY ALKALOSIS
<ol style="list-style-type: none"> 1. Increased retention of carbon dioxide in alveoli produces 2. Increased plasma H₂CO₃ which if not compensated by increase of B₂HCO₃ produces 3. Decreased pH and uncompensated acidosis 	<ol style="list-style-type: none"> 1. Increased escape of carbon dioxide from alveoli produces 2. Decreased plasma H₂CO₃ which if not compensated by decrease of B₂HCO₃ produces 3. Elevated pH and uncompensated alkalosis
<i>To compensate</i>	<i>To compensate</i>
B ₂ HCO ₃ has to increase so as to return H ₂ CO ₃ ratio toward 1:20 This can occur by: <ol style="list-style-type: none"> 1. Increasing base available for union with HCO₃ by 2. Decrease of plasma chloride through 3. Increased urinary excretion of chloride. 	B ₂ HCO ₃ has to decrease so as to return the H ₂ CO ₃ ratio toward 1:20 This can occur by: <ol style="list-style-type: none"> 1. Decreasing base available for union with HCO₃ by 2. Increased retention of a fixed anion such as 3. Retention of chloride by preferential urinary excretion of HCO₃ or accumulation of other anions such as organic acids 4. Administration of chloride appears to be indicated.
<ol style="list-style-type: none"> 1. Administration of chloride appears to be contraindicated 	

The diagnoses of respiratory acidosis and alkalosis are dependent not only on determinations of total plasma carbon-dioxide content but also of plasma pH. Whereas, in metabolic acidosis there is a correlation between the decrease in plasma carbon-dioxide content or alkali reserve and degree of acidosis, in respiratory acidosis there may be a normal or an increased plasma carbon-

dioxide content with a decrease in pH. An opposite reversal is present in respiratory alkalosis, where plasma carbon-dioxide content may be decreased or remain normal with plasma pH definitely elevated. The mechanism whereby these changes occur may be as is shown in Table I.

With the respiratory system deranged, as is the case in respiratory acidosis or alkalosis, the burden of maintaining a normal plasma pH falls more heavily on the renal mechanism. Compensation for increased or decreased H_2CO_3 is attempted by altering the B.HCO_3 so as to maintain a 1:20 ratio and thus a plasma pH of 7.4. The increase or decrease of B.HCO_3 seems to occur through an increase or decrease of the chloride excretion. However, compensation is usually not complete and an abnormal plasma pH persists. Efforts to increase the renal mechanism of compensation appear inadequate and it seems that the treatment of respiratory acidosis and alkalosis had best be directed toward the correction of the underlying pathology which is responsible for the derangement of the respiratory system.

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HEMATOLOGIC STUDIES ON CHILDREN OF Rh-NEGATIVE WOMEN COMPARED TO THOSE OF Rh-POSITIVE WOMEN

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THE importance of maternal immunization to the Rh factor as a cause of erythroblastosis fetalis has become well established in the last few years. The suggestion has also been made that occasional cases of erythroblastosis and a milder form of the disease called "icterus precox" may occur when the A-B blood group of the infant is incompatible with that of the mother. There are still those who also believe that physiologic jaundice is a result of A-B incompatibility of fetal and maternal blood. To date no satisfactory evidence has been forthcoming to show that Rh incompatibility between mother and infant is responsible for any disease process other than erythroblastosis fetalis but the question as to whether or not Rh or A-B incompatibility may be associated with subclinical erythroblastosis or an increased incidence of anemia or an increase in circulating immature erythrocytes has not been answered.

We have been interested, therefore, in attempting to find out whether infants whose blood is incompatible with that of the mother, either on the basis of Rh or A-B blood groups, have a hematologic pattern which differs in any way from those infants whose blood is compatible with that of their mothers. We have been concerned with the hemoglobin level, the number of erythrocytes, leucocytes, and normoblasts or erythroblasts present on the first day of life, and with the changes which take place by the end of the first week. The following studies were undertaken in the hope of determining if an infant whose blood is in any way incompatible with that of the mother can be expected to have a demonstrable anemia at the time of birth or if it can be expected to develop an anemia within the first eight days of life. We were also anxious to collect hematologic data which might serve as a standard for the infants delivered in The Chicago Lying-in Hospital.

A total of 244 infants born in this hospital between Jan. 1, 1946, and Dec. 31, 1946, were studied. No infant who weighed less than 2,500 Gm. or who had erythroblastosis or other known disease process was included. The first group was made up of the offspring of 149 Rh-negative mothers. These were taken at random but were consecutive in so far as laboratory facilities permitted. The choice was not influenced by the Rh of the father, and we were surprised to find that the numbers of Rh-negative and Rh-positive offspring were almost identical. The second group included the children of ninety-five Rh-positive mothers and was also composed of consecutive births in so far as possible. Only four infants in this group were Rh-negative.

Blood was obtained by heel puncture within the first twenty-four hours and again on the eighth day of life. Hemoglobin was determined by the Dick-

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Stevens photoelectric method, erythrocyte and leucocyte counts were made using standard pipettes, and blood smears were prepared with Wright's stain. The A-B blood types of the mothers and infants were established and all were classified as Rh positive or Rh negative on the basis of reaction to human anti-Rh₀ serum. Determinations for the presence of Rh antibodies were made on part but not all of the mothers. None were present in the bloods examined.

The results of the blood findings of the infants were first divided into groups according to the Rh type of the infant and his mother in the following manner:

- Group I, mother Rh negative, infant Rh positive; 75
- Group II, mother Rh negative, infant Rh negative; 74
- Group III, mother Rh positive, infant Rh positive; 91
- Group IV, mother Rh positive, infant Rh negative; 4

Frequency distribution charts were compiled for the data in the first three groups and the mean, median, and mode were determined for each. The mean was found the most statistically valid and was used throughout the study.

The standard deviation was determined for each mean value and the standard error between group 1 and 2, 1 and 3, and 2 and 3 was computed. Group 4 was not used because of the small number of cases it contained. In no instance was there a statistically significant difference (a figure greater than three times the standard error) between any two groups. It is thus apparent that the relation of the Rh of the infant to that of the mother had no effect on the blood picture either at the time of birth or in any change that occurred in the first eight days of life. (Table I.)

TABLE I. BLOOD FINDINGS IN RELATION TO RH OF MOTHER AND INFANT

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Rh of mother	-	-	+	+
Rh of infant	+	-	+	-
No. of cases	75	74	91	4
Hemoglobin (Gm.)				
first day				
mean	20.7	21.0	20.6	20.1
range*	15.7 to 25.8	15.8 to 26.2	14.4 to 26.8	
eighth day				
mean	18.6	18.9	17.8	17.7
range	13.8 to 23.4	14.5 to 23.3	12.1 to 23.5	
Hemoglobin variation (first to eighth day)				
mean	-2.3	-2.4	-2.8	-2.4
range	-2.1 to -6.8	+4.0 to -8.8	+0.6 to -6.2	
Erythrocytes (in millions)				
first day				
mean	5.95	6.11	6.40	6.60
range	4.03 to 7.87	4.33 to 7.89	4.66 to 8.14	
eighth day				
mean	5.36	5.35	5.60	5.60
range	3.86 to 6.86	3.51 to 7.19	4.06 to 7.14	
Erythrocyte variation (first to eighth day)				
mean	-0.60	-0.60	-0.90	1.00
range	+6.5 to -1.85	+1.11 to 2.31	+4.2 to -2.22	

*Range in this and succeeding tables is given as twice the standard deviation.

Since there were no demonstrable differences between infants when the blood findings were divided according to the Rh of mother and child, all data were rearranged and divided into two groups according to A-B type. The first of these, group X, included 193 infants of homospecific pregnancies (infants whose blood did not contain an A or B isoantigen lacking in the mother) and group Y, fifty-one infants of heterospecific pregnancies (infants with an A or B isoantigen not present in the mother). Frequency distribution charts were compiled for these two groups, the means were determined, and the standard deviation for each mean value was computed. The standard error between the two groups was determined and again no statistically significant differences were found.

It is thus evident that the relation of the A-B blood groups in mother and child, like the Rh, had no effect on the blood findings at birth or in the first eight days of life. (Table II.)

TABLE II. BLOOD FINDINGS IN RELATION TO A-B GROUPS OF MOTHER AND INFANT

RELATION OF INFANT'S BLOOD TO THAT OF MOTHER	X	Y
	COMPATIBLE	INCOMPATIBLE
No. of infants	193	51
Hemoglobin (Gm.)		
first day		
mean	20.7	20.6
range	26.3 to 15.1	25.4 to 15.7
eighth day		
mean	18.4	18.6
range	23.6 to 13.1	23.6 to 13.5
Hemoglobin variation (first to eighth day)		
mean	2.6	2.5
range	+1.8 to -7.0	+1.5 to -6.5
Erythrocytes (in millions)		
first day		
mean	6.20	6.17
range	8.02 to 4.38	7.85 to 4.49
eighth day		
mean	5.46	5.57
range	7.50 to 3.42	7.07 to 4.07
Erythrocytes (first to eighth day)		
mean	-0.80	-0.70
range	+0.54 to -2.14	+0.72 to -2.12

TABLE III. BLOOD FINDINGS IN 244 NORMAL INFANTS

	MEAN	RANGE
Hemoglobin		
first day	20.7	15.2 to 26.2
eighth or ninth day	18.4	13.5 to 23.3
Hemoglobin variation		
first to eighth day	2.6	+1.6 to -6.8
Erythrocytes (in millions)		
first day	6.19	4.33 to 8.05
eighth day	5.47	3.93 to 7.01
Erythrocyte variation		
first to eighth day	0.80	+0.58 to -2.18
Leucocytes		
first day	19,540	6,980 to 32,100
eighth day	11,560	5,840 to 17,280
Polymorphonuclear leucocytes		
first day	70.9%	53.7% to 88.1%
eighth day	49.2%	27.9% to 70.5%

Having shown, then, that Rh, A, or B antigens present in the blood of a child and absent in the blood of the mother do not influence the child's blood picture, all data were reassembled in order to determine the mean values for the entire group. (Table III.)

TABLE IV. NORMOBLASTS PER 100 LEUCOCYTES ON THE FIRST AND EIGHTH DAYS OF LIFE

Rh of infant in relation to Rh of mother	INCOMPATIBLE		COMPATIBLE		TOTAL	
	INCOM- PATIBLE	COM- PATIBLE	INCOM- PATIBLE	COM- PATIBLE	NO.	%
A-B of infant in relation to A-B of mother						
Number of normoblasts on first day of life						
0	8	51	24	88	171	70.0
1	3	4	7	19	33	13.5
2	0	4	5	11	20	8.2
3	0	1	1	5	7	2.9
4	0	0	1	2	3	1.2
5	0	2	0	0	2	0.9
6-10	1	2	1	3	7	2.9
11-20	0	0	0	1	1	0.4
Number of normoblasts on eighth day of life						
0	12	64	39	128	243	99.6
1	0	0	0	1	1	0.4
Total cases	12	64	39	129	244	100.0

TABLE V. RELATION OF A-B BLOOD GROUP TO Rh OF MOTHER AND INFANT

A-B BLOOD GROUP		MOTHER Rh - INFANT Rh +	MOTHER Rh - INFANT Rh - OR MOTHER Rh + INFANT Rh - OR MOTHER Rh + INFANT Rh -	TOTAL
MOTHER	INFANT			
A	A	18	40	58
A	O	6	15	21
A	B	0	4	4
A	AB	2	6	8
B	B	6	6	12
B	O	5	5	10
B	A	0	6	6
B	AB	2	4	6
AB	AB	1	0	1
AB	A	3	5	8
AB	B	2	2	4
AB	O	0	0	0
O	O	23	56	79
O	A	4	12	16
O	B	4	7	11
O	AB	0	0	0
Total		76	169	244
Incompatible A-B		12 (15.0%)	39 (23.2%)	51 (20.9%)
Compatible A-B		64 (85.0%)	129 (76.8%)	193 (79.1%)

Examination of blood smears failed to show any difference in the number of immature blood cells in the circulation in the compatible and incompatible groups. Seventy per cent had no immature erythroblasts and over 90 per cent had two or less. In only one case were more than ten present on the first day of life and this was an infant which was compatible with its mother both in relation to Rh and A-B. One normoblast was found in the blood of one infant on the eighth day; none had been found in the smear made on the first day. In no other instances were nucleated red blood cells found on the eighth day during the course of counting 100 leucocytes. (Table IV.)

When the infants and mothers were arranged according to A-B blood groups, it was found that a somewhat greater number were incompatible on the basis of A-B blood groups among those who were compatible on the basis of Rh than among those who were incompatible. In the entire group 20.9 per cent were incompatible on an A-B basis. (Table V.)

SUMMARY

Hemoglobin estimations, erythrocyte, leucocyte, and differential counts were made on the first and eighth days of life on the blood of 244 infants. When the results were classified according to the compatibility of the A-B and Rh factors of the mother and child, no hematologic differences were demonstrable between those in which the infant's blood was compatible with that of the mother and those in which it was incompatible. Both groups were combined to give normal mean values for the first and eighth days of life.

BACTERIAL FLORA IN EYES OF NEWBORN INFANTS DURING FIRST FORTY HOURS OF LIFE

AFTER SINGLE INSTILLATION OF PENICILLIN AND SILVER NITRATE

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IN a previous communication,¹ penicillin was compared clinically with silver nitrate for prophylaxis against ophthalmia neonatorum. Penicillin was used by a multiple instillation method.

The present study was done to determine the bacterial flora of the conjunctival sac after prophylaxis, using only a single instillation of penicillin; to compare the results with those after silver nitrate prophylaxis; and to determine whether the bacterial flora of the conjunctiva was changed during the first forty hours of life.

METHODS OF PROPHYLAXIS

Prophylaxis was carried out in the delivery room within one hour after birth, and before the infant went to the nursery.

When penicillin was used, the eyelids and adjacent face area of the newborn infant were cleansed of contaminating secretions by gently wiping with a large cotton ball from the inner canthus outward. The eye was closed at the time. Gauze was then used on the fingers for traction to open the eyelids while each eye was flushed thoroughly with about 2 or 3 c.c. of sterile normal saline solution. One drop of penicillin solution was then instilled into the conjunctival sac of each eye.

Silver nitrate prophylaxis was carried out in the same manner as described above, except that sterile distilled water was used for flushing the eyes, after which one drop of silver nitrate was instilled instead of penicillin.

Penicillin was used in the form of the crystalline sodium salt of penicillin in a concentration of 2,500 units per cubic centimeter of normal saline. Silver nitrate was employed as a one per cent solution in distilled water.

PROCEDURE

The following study was done during the period in which penicillin was used as a prophylactic agent, and then repeated during the period in which silver nitrate was used. In each study, the eyes of ten infants were cultured during the interval of zero to four hours after the prophylactic treatment was given.

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Groups of ten infants were then cultured for the first forty hours at four-hour intervals. Thus, the eyes of 100 infants were cultured after each method of prophylaxis. The infants were unselected except that no infant was included whose eyes exhibited pus. Eighty-three per cent of the infants were Negro and 17 per cent white.

BACTERIOLOGIC PROCEDURES

Cultures were taken from the conjunctival sac of each eye of each infant studied. A separate sterile swab contained in a specimen tube was used for each eye, and both swabs were inserted into a sterile specimen tube containing approximately 2 cc of tryptose broth. The two swabs were immediately streaked across the surface of two plates containing McLeod's medium for isolation of the gonococcus, two blood agar plates, and one eosin-methylene blue agar plate. The broth in the specimen tube was then distributed in approximately equal portions into two tubes of blood tryptose broth.

PENICILLIN

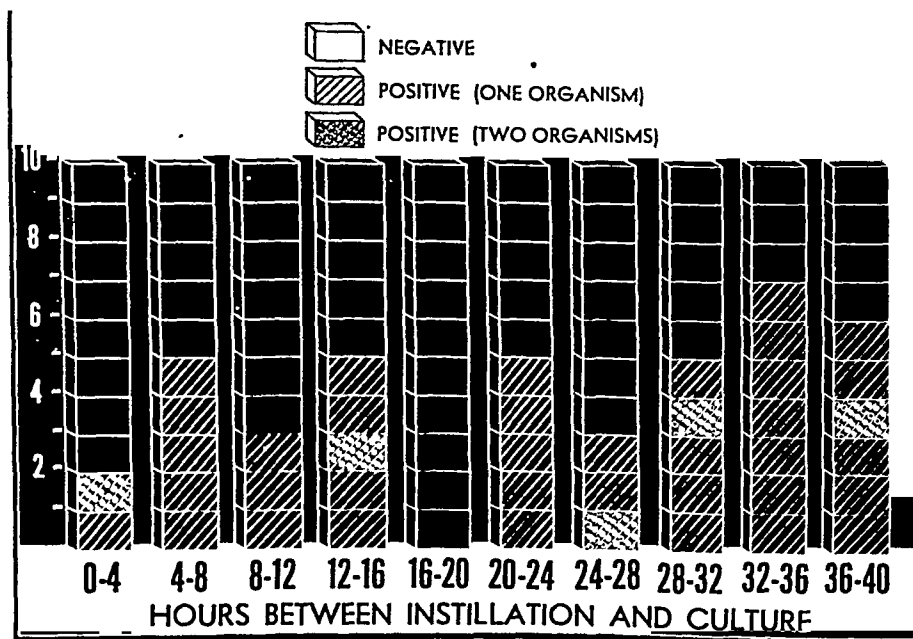


Fig. 1—Conjunctiva cultures from 100 newborn infants at varying intervals after single instillation of penicillin. Each square represents one infant.

One tube of blood tryptose broth, one blood agar plate, and the eosin-methylene blue agar plate were incubated at 37.5° C. The other tube of blood tryptose broth and the second blood agar plate were sealed in an earthenware jar, using the Varney method for detecting anaerobic organisms, and incubated at 37.5° C. The two plates of McLeod's medium were sealed under 10 per cent carbon-dioxide tension, using the method of Wadsworth,² and incubated at

37.5° C. The container was a screw-top five-pound coffee jar which possessed an inner top with a rubber ring to aid in sealing.

At the end of twenty-four hours, the two blood agar plates, the eosin-methylene blue agar plate, and the two culture tubes of blood tryptose broth were examined. If negative, they were examined again at the end of forty-eight hours. At the end of forty-eight hours, the two plates of McLeod's medium were examined for colonies of *Neisseriae*. All plates which were negative after forty-eight hours of incubation were discarded. All broths which were negative after forty-eight hours of incubation were retained and re-examined five days after the specimen was collected. At the end of this period, if the broths were still negative, the culture was considered negative. If positive, the broths were streaked on plates and identification of the organism or organisms was made.

SILVER NITRATE

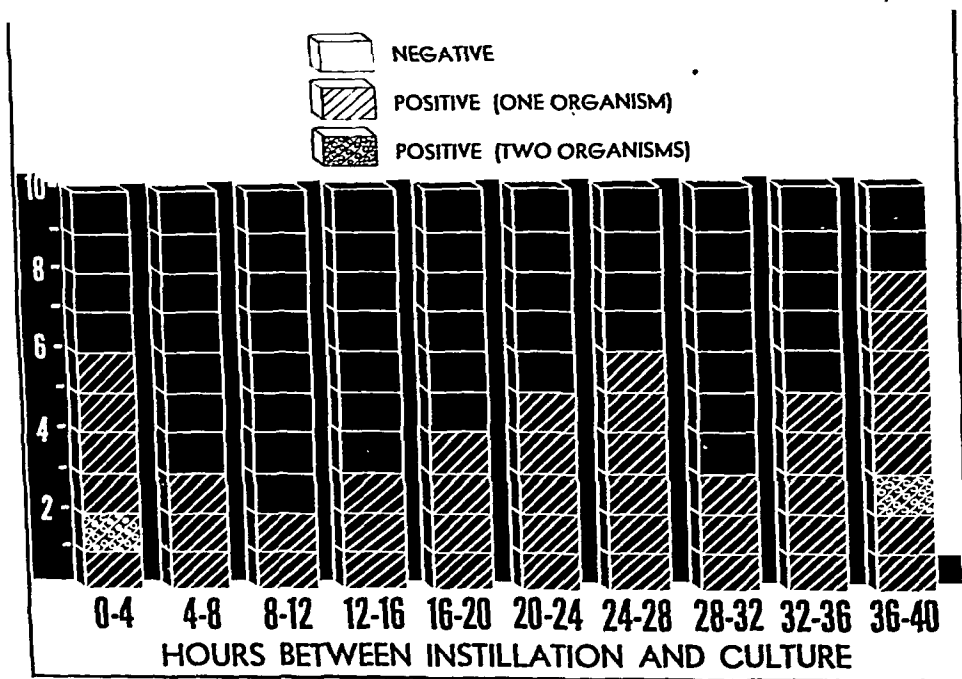


Fig. 2.—Conjunctiva cultures from 100 newborn infants at varying intervals after single instillation of silver nitrate. Each square represents one infant.

Organisms were studied as to microscopic appearance and colony formation. Staphylococci were classified as to their pigment formation, and their capacity for hemolyzing blood and coagulating plasma. The bile solubility test was used to differentiate between *Streptococcus viridans* and the pneumococcus. Gram-negative rods were grouped as to motility, pigment formation, ability to form spores, and action on carbohydrates. Gram-positive rods which gave the microscopic appearance of *Corynebacteria* were inoculated to carbohydrate broths to differentiate xerose, hofmannii, and diphtheriae. All yeasts were incubated on

carbohydrate broths for identification. When colonies suggestive of *Neisseriae* were found on the plates containing McLeod's medium, they were tested for the "oxidase reaction." Colonies giving a positive reaction were transferred to tubes of dextrose, maltose and saccharose media which were incubated for forty-eight hours under 10 per cent carbon-dioxide tension to differentiate the varieties of *Neisseriae*.

TABLE I. INCIDENCE OF POSITIVE CULTURES FROM CONJUNCTIVA AFTER SINGLE INSTILLATION OF PENICILLIN AND SILVER NITRATE

PENICILLIN		SILVER NITRATE	
NUMBER OF INFANTS	POSITIVE CULTURES	NUMBER OF INFANTS	POSITIVE CULTURES
100	41	100	45

TABLE II. TYPE AND INCIDENCE IN RELATION TO TIME OF ORGANISMS FOUND IN POSITIVE CULTURES AFTER PENICILLIN PROPHYLAXIS DURING FIRST FORTY HOURS OF LIFE

ORGANISMS	HOURS BETWEEN PENICILLIN INSTILLATION AND CULTURE										TOTALS
	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	
<i>Staphylococcus aureus</i>											
hemolytic, plasma coagulase negative	~	1	2	-	-	1	-	1	3	-	
nonhemolytic, plasma coagulase negative	~	-	-	2	-	-	1	-	1	1	
<i>Staphylococcus albus</i>											
hemolytic, plasma coagulase negative	~	-	-	-	-	-	-	-	1	1	
hemolytic, facultative aerobe, plasma coagulase negative	~	-	-	-	-	1	-	-	-	-	
nonhemolytic, plasma coagulase negative	~	1	-	2	~	1	-	1	1	3	
<i>Staphylococcus citreus</i>											
nonhemolytic, plasma coagulase negative	~	-	-	-	-	-	-	-	1	-	26
<i>Streptococcus</i>											
beta-hemolytic, anaerobic	1	-	-	-	-	-	-	-	-	-	
nonhemolytic	~	-	-	-	-	-	-	-	-	1	
nonhemolytic, anaerobic	1	1	-	1	-	-	-	-	-	-	
nonhemolytic, facultative aerobe	~	-	-	-	-	1	-	-	-	-	6
<i>Escherichia coli</i>	-	-	-	-	-	-	1	2	-	-	3
Gram-positive sporulating bacillus, unclassified	~	-	-	-	-	-	1	2	-	-	3
<i>Corynebacterium hoffmannii</i>	1	-	-	-	-	-	1	-	-	-	2
<i>Bacterium aerogenes</i>	-	1	-	-	-	1	-	-	-	-	2
<i>Pseudomonas pyocyanea</i>	-	1	-	-	-	-	-	-	-	-	1
<i>Diphtheroid</i> , unclassified	~	-	1	-	-	-	-	-	-	-	1
<i>Bacterium faecalis alcaligenes</i>	-	-	-	1	-	-	-	-	-	-	1
Gram-negative sporulating bacillus, facultative anaerobe, unclassified	~	-	-	-	-	-	-	-	-	1	1
Totals	3	5	3	6	0	5	4	6	7	7	46

RESULTS

Positive cultures were obtained in 41 per cent of the 100 infants studied after the use of penicillin and in 45 per cent of the 100 infants studied after the use of silver nitrate (Table I).

After the use of penicillin, forty-six organisms were isolated in the forty-one positive cultures. The type and incidence of these organisms in relation to time of appearance are tabulated in Table II. After the use of silver nitrate, forty-seven organisms were isolated in the forty-five positive cultures. These organisms in relation to time are tabulated in Table III.

When the results are represented graphically in relation to time after the use of penicillin (Fig. 1), a tendency is seen for the number of positive cultures to increase. Thirty per cent of the cultures are positive during the first twenty hours of life as compared to 52 per cent during the following twenty hours.

TABLE III. TYPE AND INCIDENCE IN RELATION TO TIME OF ORGANISMS FOUND IN POSITIVE CULTURES AFTER SILVER NITRATE PROPHYLAXIS DURING FIRST FORTY HOURS OF LIFE

ORGANISMS	HOURS BETWEEN SILVER NITRATE INSTILLATION AND CULTURE										TOTALS
	0-4	4-8	8-12	12-16	16-20	20-24	24-28	28-32	32-36	36-40	
<i>Staphylococcus aureus</i>											
hemolytic, plasma											
coagulase negative	-	-	1	1	1	-	-	-	-	1	
hemolytic, plasma											
coagulase positive	-	-	-	-	-	-	1	-	-	-	
nonhemolytic, plasma											
coagulase negative	-	-	-	1	1	1	1	1	2	1	
nonhemolytic, plasma											
coagulase positive	-	-	-	-	-	-	-	-	-	1	
<i>Staphylococcus albus</i>											
hemolytic, plasma											
coagulase negative	1	-	-	-	-	-	-	1	-	-	
nonhemolytic, plasma											
coagulase negative	4	3	1	1	-	3	1	-	3	2	
nonhemolytic, plasma											
coagulase positive	-	-	-	-	-	-	-	-	-	1	
<i>Staphylococcus citreus</i>											
nonhemolytic, plasma											
coagulase negative	-	-	-	-	-	-	1	-	-	-	
nonhemolytic, plasma											
coagulase positive	-	-	-	-	-	-	-	-	-	1	
<i>Streptococcus</i>											
beta-hemolytic facul-											
tative anaerobe	-	-	-	-	-	-	1	1	-	-	
beta-hemolytic, facul-											
tative aerobe	-	-	-	-	-	-	-	-	-	1	
nonhemolytic	-	-	-	-	-	-	1	-	-	-	
nonhemolytic, anaerobic	1	-	-	-	1	-	-	-	-	-	6
<i>Bacterium aerogenes</i>	-	-	-	-	1	-	-	-	-	-	1
Gram-negative sporu-											
lating bacillus, anaerobic unclassified	1	-	-	-	-	-	-	-	-	-	1
Gram-positive sporulat-											
ing bacillus, unclassified	-	-	-	-	-	1	-	-	-	-	1
Member of Colon-											
aerogenes group	-	-	-	-	-	-	-	-	-	1	1
Totals	7	3	2	3	4	5	6	3	5	9	47

When the results are presented graphically after the use of silver nitrate (Fig 2), this same tendency of positive cultures to increase with time is seen. Thirty-six per cent are positive during the first twenty hours and 54 per cent are positive during the following twenty hours.

Seven anaerobic organisms (7.5 per cent) were encountered out of a total of ninety-three. Four of these were found after penicillin prophylaxis and three after silver nitrate. Four of the seven were isolated during the first four hours, and all were isolated during the first twenty hours.

The gonococcus was not isolated from any culture.

COMMENT AND CONCLUSIONS

The bacterial flora in the eyes of 200 infants was studied during the first forty hours of life. One hundred were studied after prophylaxis employing a single instillation of penicillin, and 100 after a single instillation of silver nitrate.

The number of positive cultures was slightly less after penicillin prophylaxis (41 per cent) than after silver nitrate (45 per cent). The total number of organisms encountered in each group was approximately the same. A tendency was observed in each group for the number of positive cultures to increase with time.

That anaerobic organisms are encountered in the conjunctiva only during the first hours of life is to be expected. The oxygen tension in the conjunctival sac produces conditions unsuitable for growth.

This study indicates by bacteriologic findings that penicillin, when used as a single instillation, compares favorably with silver nitrate as a prophylactic agent, and that penicillin in this series was slightly better than silver nitrate in depressing the bacterial flora of the newborn conjunctiva during the first forty hours of life.

Further study is required for interpretation of the observed increase of the bacterial flora with time in the conjunctiva of the newborn infant.

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THE USE OF SERUM GAMMA GLOBULIN ANTIBODIES TO CONTROL CHICKEN POX IN A CONVALESCENT HOSPITAL FOR CHILDREN

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THE entrance of a person with a contagious disease into a children's hospital of a convalescent home always disorganizes the institution. A review of the patients' charts is imperative to determine those who are susceptible to the disease. The victim of the contagious disease must be transferred to his home, thus exposing others, or he must be sent to a contagious hospital. Strict quarantine must be enforced in the ward or institution in which the contagion was found, and no new admissions can be permitted until the incubation period has passed.

Chicken pox often enters institutions in spite of all preventive efforts. While it is usually not a dangerous disease, it is one of the most contagious of the exanthemata. It is difficult to isolate and may be infectious for a prolonged period. Therefore, if new admissions of unprotected children are allowed, there may be sporadic incidents for weeks.

The administration of adequate doses of pooled adult serum at the proper time to children who had definitely been exposed to measles has long been recognized as a means of modifying or preventing the development of the disease. More recently, immune serum globulin (human) has been accepted as a method for modifying or preventing measles. A test of its efficacy as a method of modifying or preventing chicken pox seemed advisable.

An opportunity to make such a test was presented when an inmate of a crippled children's convalescent hospital in Atlanta developed chicken pox. It was decided to attempt to control the spread of the disease by administering human immune globulin to all exposed children in the institution who had not had chicken pox. The child ill with the disease was transferred to the contagious hospital. Seven patients who had never had chicken pox received 2 c.c. serum globulin intramuscularly. None developed the disease, but no new admissions were permitted for eighteen days.

Seven months later, chicken pox again made its appearance in the institution. From previous experience, it seemed reasonable to keep the patient in the institution and give the serum globulin to all who might be susceptible. At the time, fifteen children had not had the disease, and these were given 2 c.c. serum globulin within twenty-four hours after the first diagnostic symptoms were recognized. Four of these came down with the disease in one, two, three, and six days, respectively, and these cases of chicken pox were not modified. As the incubation period is considered fourteen to eighteen days, these patients must have gotten the infection at about the same time and probably from the same source as the child who first showed manifestations of the disease. One very mild case developed fourteen days after the administration of the serum globulin. This could be considered one failure, even though the disease was apparently modified by the administration of the serum globulin.

A child admitted to the institution during the incubation period of chicken pox developed a case nineteen days later, though the serum globulin had been given. Another patient, to whom the serum globulin was not administered because he was said to have had chicken pox, developed the disease nineteen days later.

After several months free from contagion, a 3-year-old child was admitted to the hospital. During the night he developed a temperature of 104° F. and the following day he began to erupt with typical lesions of chicken pox. To confirm or disprove the previous experience with the administration of immune globulin (human), the patient was not sent to the contagious hospital nor isolated in any way. In the ward with this child were nine children varying in age from 3 months to 3½ years, none of whom had previously had chicken pox. Those under one year of age were given 2 c.c. of the immune globulin within twenty-four hours after the chicken pox was diagnosed; those over a year of age were given 3 c.c. None of these developed chicken pox.

The same day the case was discovered, the seven inmates of an adjoining room, varying in age from 4 to 8 years, who had not had chicken pox, were given 3 to 4 c.c. immune serum globulin, depending on age. Though these had the same night nurse, were at the same play table, and used the same bath, none contracted the disease.

In another room on the same floor the seven children of an older age group who had not had chicken pox were given 5 c.c. of the immune serum. None of these contracted the disease. All on this floor had the same nurses and used the common hallways, playgrounds, and schoolrooms.

On another floor were ten older children, eight of whom had had chicken pox. The two who had not had the disease were given 5 c.c. of the immune serum globulin. Neither of these contracted the disease.

Now no restrictions were placed on new admissions. To the six children admitted during the following nineteen days, immune serum globulin was administered, 2 to 5 c.c., depending on age. None developed the disease. After the usual incubation period of twenty-one days had passed, no new admissions were given the immunization.

Two months after this episode a 13-year-old girl who had been in the institution for a week and had a case history of having had the chicken pox developed the disease. She was not removed from the hospital or quarantined. As all the inmates had been given the immune globulin or had a history of having had the disease, none were given the immune globulin. A 14-year-old girl who said she had had chicken pox developed a typical case eighteen days later. The same procedure was followed as in the previous case, that is, no removal or isolation.

The advisability of repeating the administration of the immune globulin for fear that the passive immunity may have been exhausted was under consideration. This was answered by the entrance of a case of measles. All inmates were given the immune globulin. The case of measles was sent to the contagious hospital. No cases of measles or chicken pox developed.

Six months later a child admitted to the hospital developed chicken pox within twenty-one days. The following day, a child who had been in the institution since the previous cases of chicken pox, and who had had the immune

globulin, developed a typical case. There had been no known exposure, though a visitor might have brought in the infection or a mild case may have been overlooked. It does not seem reasonable that a carrier or delayed eruption could have survived six months. But the fact that one of the children who had been given the immune globulin now developed chicken pox when it had been protected six months seems to indicate that the immunity is exhausted in six months.

Again the same procedure was followed—no isolation or quarantine. The sixteen children who had not had the disease were given the immune globulin in the same doses as the previous cases within twenty-four hours. During the accepted incubation period of twenty-one days, sixteen admissions gave a history of not having had chicken pox. These were given the immune globulin. Eleven days after the eruption of chicken pox, ten days after the administration of the immune globulin, one child developed a mild case. The nurse counted six lesions but they were typical. There was no febrile reaction. Nineteen days after the chicken pox was noticed and eighteen days after the immune serum had been given, another child developed a typical case. This was definitely a failure. None of the children admitted during the incubation period and given the immune globulin developed the disease.

TABLE I

PATIENTS GIVEN GLOBULIN	NO. DEVELOPING CHICKEN POX AFTER EXPOSURE				UNPRO- TECTED	PRO- TECTED	% PRO- TECTED
	1 DAY	2 DAYS	6 DAYS	10 DAYS			
First episode 7	0	0	0	0	0	7	100
Second episode 16	1	1	1	0	2	11	85.5
Third episode 31	0	0	0	0	0	31	100
Fourth episode 23	0	0	0	1	1	21	91
Total, 77	1	1	1	1	3	70	95.8

SUMMARY AND CONCLUSION

There were four separate episodes of chicken pox in a convalescent hospital for crippled children. All unprotected children, those who had not had chicken pox, were given immune serum globulin in doses as follows:

Under one year of age, 2 c.c.

Two to 4 years of age, 3 c.c.

Four to 6 years, 4 c.c.

Over 6 years, 5 c.c.

Of the seventy-seven given the immune globulin, if the accepted incubation period is fourteen to twenty-one days, there were three failures. Seventy children were protected.

A single case of chicken pox developed, one, two, six, and ten days after the administration of the immune globulin. This experience seems to justify the conclusion that the administration of immune serum globulin (human) is of value in institutions and in selected instances when it is deemed advisable to modify or prevent chicken pox.

DOES PERTUSSIS ACTIVATE TUBERCULOSIS?

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SOME physicians contend that pertussis superimposed on active or latent tuberculosis leads to a rapid dissemination of the latter and a poor prognosis.

Many of the papers which have been written in South America, Germany, and France give the clinical impression that infectious diseases, and especially pertussis and rubella, are phthisiogenic, particularly in children. Without adequate proof and without detailed data, it has been stated that most of the fatalities in whooping cough are due to tuberculous pneumonia. Those who have said this believe that because of the enlarged thoracic glands and the continued exhausting type of cough, active or latent tuberculosis is spread through the lungs.

Some observers, Ledbetter and White,¹ and Eddy and Mitchell,² hold the opposite view—that is, that pertussis per se plays no active role in the activation or dissemination of tuberculosis. Morissette reported an epidemic of pertussis in a tuberculosis sanatorium for children and observed that the attack of pertussis was of short duration, of slight severity, and without sequelae, although the epidemic in the local community was unusually severe.

In a study of 2,000 cases of pertussis observed over a period of three years in Vienna, where there is a high incidence of tuberculosis, Gabriel⁴ analyzed the clinical and the post-mortem findings and showed that pertussis practically never increased the activity of tuberculosis nor activated the latent form. This has also been our impression at the Cleveland City Hospital. Interest in this subject was stimulated by the following case.

N. S., a 5-year-old white girl, was admitted to the Department of Contagious Diseases, City Hospital, Cleveland, on Jan. 10, 1946. The admission diagnoses were pertussis and pneumonia. According to the history, the pneumonia occurred on Dec. 1, 1945, and the child was treated with sulfadiazine. About December 15, chickenpox developed and cleared in the usual length of time, but a coryza and purulent otitis media remained. On Jan. 1, 1946, she began to whoop. She was given rabbit antipertussis serum on January 3, but the whooping cough persisted and became worse. She was admitted to the hospital on January 10, and the diagnoses of pertussis and severe bronchopneumonia were confirmed. A cough plate was positive for *Hemophilus pertussis*, and the diagnosis of bronchopneumonia was substantiated by x-ray. A tuberculin test, 1:1,000, was negative. The patient was given additional antipertussis antiserum, but despite all therapy the course was slowly downhill and death occurred on Feb. 5, 1946. The clinical diagnoses were pertussis, bilateral bronchopneumonia, and cor pulmonale. The pathologic diagnosis was diffuse, disseminated, miliary tuberculosis.

From the Jack and Helntz Laboratory, Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland.

Post-mortem examination done by Dr. John Robertson revealed the body of a well-developed and well-nourished 5-year-old white girl. The heart was enlarged, weighing 125 Gm. (expected weight, 85 Gm.); the pericardium was smooth and glistening, containing 80 c.c. of straw-colored fluid with a specific gravity of 1.010; the ventricular walls were thickened, the left measuring 12.5 mm., the right 4.5 mm. The lungs were voluminous, pink, and firm without normal crepitation, and the surfaces were studded with innumerable fine nodules measuring from 2 mm. to 3 mm. in diameter, some areas being conglomerate and measuring as much as 6 mm. in diameter; all were grayish white and raised above the surrounding surfaces with no evidence of caseation or calcification. Bronchopulmonary lymph nodes near the hilum showed caseation and fibrosis, and the nodes at the tracheal bifurcation were of rubbery consistency with central caseation being present. The bronchi contained a glairy mucinous material. There was bronchogenic tuberculosis of the lungs. The bronchi and bronchopulmonary lymph nodes showed focal fibrosis and calcification consistent with the diagnosis of healed tuberculosis of the lymph nodes.

The liver, extending 4 cm. below the costal margin, was enlarged, weighing 875 Gm. (expected weight, 596 Gm.), and its surface was studded with innumerable grayish white, flat lesions measuring from 1 mm. to 2 mm. in diameter. It was sectioned with average resistance and had throughout the same grayish white nodulation as was present on the surface.

The spleen was enlarged and weighed 75 Gm. (expected weight, 47 Gm.). The capsule was smooth and glistening, but numerous grayish white, flat lesions could be seen through it. These varied from 1 mm. to 2 mm. in diameter. On section of the spleen, the same lesions were seen throughout the splenic tissue. The remainder of the examination was essentially negative.

Microscopic examination of the liver and spleen revealed miliary tuberculosis. The bronchi and bronchopulmonary lymph nodes showed conglomerate caseous tuberculosis.

At first hand, this would seem to be an instance where pertussis contributed to or had excited tuberculosis.

Careful review of the family history and additional interviews with the family disclosed some hitherto unknown facts. The child had visited in Cleveland from May to September, 1945, in a home where there was an adult ill with active tuberculosis. Another child from a different family, exposed to the same contact, had questionable active tuberculosis. When the members of the patient's (N. S.) family moved to Cleveland in October, 1945, they resided at the house where the individual with active tuberculosis had previously lived. In addition, our patient had been in intimate contact with a child with active tuberculosis during November, 1945.

The findings were interpreted as showing organization of the mediastinal lymph nodes, placing the exposure at least as far back as November, 1945. The reaction to the tuberculin test was negative, but there probably was a slight delay in the production of the allergic phase. It is doubtful whether in this instance pertussis per se had activated or even caused dissemination of tuberculosis. It was felt that the patient would have evidenced miliary tuberculosis

and progressed as she did even if she had not had the infection of *H. pertussis*.

It could not be denied, however, that our previous conceptions were shaken, and in order to throw some light on the subject, all cases of pertussis admitted to the Contagious Hospital from 1938 to Aug. 1, 1947, were reviewed.

Since 1926, patients ill with pertussis have been routinely tested with tuberculin, since a tuberculous pulmonary infection without pertussis may simulate pertussis even to the whoop. Curiously enough, it has been shown that the evidence obtained on x-ray examination of the lungs of a patient ill with whooping cough, or measles at the height of the rash, cannot at times be differentiated from that produced by miliary tuberculosis. The reaction to the tuberculin test is, therefore, necessary information.

There were 1,747 patients admitted with pertussis. In thirty-eight patients there was some connection with tuberculosis, and these constituted the basis for the present investigation. In twenty-three, the reaction to the tuberculin test was positive, in one instance, one week after admission; in the remainder, it was negative.

In nineteen patients, a clinical diagnosis of tuberculosis, either primary or active, parenchymatous, or arrested had been made (two cases being discovered on or a few days after the patients' admission). All of these patients had a positive reaction to the tuberculin test.

The children tested were usually infants, the age range of this group (nineteen) being from 7 months to 7 years, the mean age being 13 months; 7 were whites and 12 were Negroes. Unquestionably, all but one had pertussis. The history of this one patient will be given in detail later. Three children were older and had no evidence of active tuberculosis. The twenty-third case was that of N. S., just discussed.

An analysis of the nineteen cases was made in order to show the effect, if any, of pertussis on tuberculosis.

Group I.—Nine of the nineteen patients who had pulmonary tuberculosis were found by x-ray examination to have primary active complexes without parenchymatous involvement. All nine of these patients were followed for at least one month in the hospital and for varying lengths of time after discharge. None showed any reactivation with parenchymatous spread of the primary complex. In eight of these nine patients, the primary complex showed healing even while the patient was confined to the hospital, in spite of clinically severe pertussis. The remaining patient was followed in the Outpatient Department and was completely healed in six months.

Group II.—X-ray examination of the nine remaining patients who unquestionably had pertussis showed a more diffuse tuberculous infection on admission, either tuberculous pneumonia or an infiltration too large to be considered a primary focus. Four of these patients were transferred from a sanatorium where they had been undergoing treatment for tuberculosis, and were returned to the sanatorium after recovering from pertussis. In all patients there was continued healing of the tuberculosis in spite of the pertussis; in no patient was there a delay in the healing process. It seems fair to assume that pertussis

did not cause the spread of the tuberculosis. Although this was a small series, the patients were intensively studied clinically and numerous x-ray examinations were made.

In four out of the nine cases in Group II, active pulmonary tuberculosis was diagnosed for the first time on admission. In all four of these patients, there was demonstrated acute, progressive, untreated tuberculosis. Two of the patients had been exposed to the active disease at home; one patient on admission had tuberculous cervical lymphadenitis. In all there was some spread of the tuberculous process while in the hospital. In two patients this did not occur until clinical recovery from the pertussis was apparent. All four patients were treated for tuberculosis after the attacks of pertussis.

In none of these patients was the pertussis of the severe exhausting type with prolonged weeks of coughing, which some observers state is the type which fosters tuberculosis. In three of the four patients, it was possible to deduce that the active tuberculous process preceded the infection with whooping cough. In none of the cases was the tuberculous process accelerated or very severe. All recovered completely, the tuberculosis having been apparently arrested after two years. None of the patients had miliary tuberculosis. Thus, it might be stated that the tuberculosis ran its expected course unaltered by pertussis.

The remaining nineteenth patient had tuberculosis on admission. Her history is as follows:

G. H., an 11-month-old Negro child, was admitted to the hospital on Jan. 18, 1947, because of whooping cough. Her mother insisted that she had not been exposed to whooping cough and had developed a cough with paroxysms only four days before admission. Three days before admission, she started to vomit and cough and had emesis and fever until admission. The incubation period was too short for whooping cough (one day), and a tuberculin test (1:1,000), which was negative, was done on Jan. 23, 1947. The white blood count was 26,400, 84 per cent of which were lymphocytes. The patient had a paroxysmal cough with respiratory whoop, and the lungs were filled with coarse rhonchi. The liver was slightly enlarged.

There was no history of exposure to pertussis. It was thought there was some evidence of pneumonia, and an x-ray on January 23 showed it to be present in the right upper lung. We did another tuberculin test in a dilution of 1:1,000 on Jan. 30, 1947, and this time it was positive. The histoplasmosis test was negative.

On March 9, cross-infection of measles occurred. On March 20, the x-ray showed miliary tuberculosis, and the spleen was palpable on this day. Streptomycin was started, but on Sept. 1, 1947, the x-ray showed no appreciable change. Pneumonia, as well as miliary tuberculosis, persisted in the right side of the chest, although the patient had been afebrile for seven days and had not received streptomycin for thirty days.

A second child at home, 3 years and 3 months of age, developed pertussis and was admitted to the hospital a few weeks later. This child, the mother, and the father had negative reactions to the tuberculin test, and their x-ray examinations were also negative. There was no history of exposure to tuberculosis.

All members of the family were well. The only possible predisposing factor was that the child (G. II.), when 3 weeks of age, and for three months thereafter, had lived in a crowded rooming house.

Was this patient one in whom tuberculosis was initiated by whooping cough or rubeola, or was she one who had a tuberculous infection that progressed in the usual manner? This question cannot be answered. It can be said that the child had tuberculosis before the onset of the whooping cough. Based on the fact that it takes from three to six weeks for the tuberculin reaction to become positive after infection, the child would have had the tuberculosis at least four weeks before admission, but for how much longer could not be determined, nor in this instance could one state what effect whooping cough and rubeola had on the patient's condition. She seemed to have progressed as would a patient with an ordinary infection of tuberculosis.

In the fifteen patients who had negative reactions to the tuberculin test, the diagnosis of tuberculosis was questionable and the x-ray evidence cleared as soon as did the whooping cough.

Many other patients over 5 years of age (fifty-six) who had positive tuberculin tests but no signs of pulmonary involvement, negative x-ray findings, negative family history of exposure, etc., remained well. They were not included in this report.

COMMENTS

X-ray films of the chest may show evidence of lesions which are often wrongly diagnosed as being due to tuberculosis. This is a common mistake.

In eight out of nine patients with primary active complexes there was no worsening of the active tuberculous process during or after infection with *H. pertussis*. In four patients, diagnosed for the first time on admission as having pulmonary tuberculosis, there was some spread of the disease while they were ill with pertussis. It was assumed that this was the natural course of the tuberculous infection based on the experience with this disease in a local sanatorium.

SUMMARY

There were 1,747 patients with pertussis admitted to the Cleveland City Hospital between January, 1938, and Aug. 1, 1947. In thirty-eight patients, an x-ray diagnosis of a suspicious tuberculous lesion was made. Twenty-three had positive reactions to the tuberculin test; three of the latter were in older children with negative x-ray findings, while nineteen actually had tuberculosis (excluding the patient, N. S., on whom an autopsy was performed). In no instance, save in the case of G. II., reported in detail, could any evidence be found on which to base the conclusion that the tuberculosis was activated by the pertussis. It cannot be said that pertussis does not possibly activate this disease, but all evidence is to the contrary, and the burden of proof rests on the shoulders of whoever makes this assertion. Certainly it is clear that reactivation of tuberculosis following pertussis is so rare that it is probably a coincidence.

CONCLUSIONS

Every patient ill with whooping cough, especially Negro children, should have a tuberculin test at the onset of the pertussis.

Every patient ill with whooping cough who coughs longer than a month should have another tuberculin test, for if he does not have bronchiectasis, he may have tuberculosis.

In the presence of acute whooping cough or measles, an x-ray diagnosis of miliary tuberculosis can never be made if the reaction to the tuberculin test is not known.

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FOOD ALLERGY

IV. THE FUNCTION AND CLINICAL APPLICATION OF THE ROTARY DIVERSIFIED DIET

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IT HAS been said, "from time immemorial the diet has been the cure of almost every illness, yet it has seldom proved successful in the treatment of any disease or syndrome." This statement is not a condemnation of the possible effectiveness of diet as a means of therapy, but it does emphasize two important facts. First, the constantly recurring implication that diet may be an etiologic factor in various syndromes indicates there have been many observations pointing to this probability. Second, it suggests that the clinical application of dietary manipulation may not have been carried out in a correct manner.

In this presentation I wish to discuss the function and the use of the rotary diversified diet as a therapeutic measure in allergic syndromes, to delineate the indications for its use, and to point out the pitfalls which might make its application ineffective.

I. THE NATURE OF THE ROTARY DIVERSIFIED DIET

In the case of allergy, diet may be used either as a diagnostic or as a therapeutic procedure. Rowe's³ elimination diets are the most common ones used for the diagnosis. Gay¹ has advocated a diagnostic diet which was based on our principle of performing individual food tests, that is, a diet in which all foods are used but once in five days. Little can be found in the literature concerning diet as a therapeutic measure in the field of allergy.^{2, 4} Such references do not give any details which would enable the reader to apply the dietetic procedures with accuracy. One can hardly apply the term "therapeutic diet" to the blanket indictment of "nuts," "fish," or "candies," as is often routinely done when advising patients concerning choice of foods in the case of asthma or hay fever.

I gave some of the details of this diet at the Allergy Forum in Cleveland, in 1940, and excerpts were published in *Science News* at that time. I also detailed this procedure at the St. Paul meeting of the American College of Physicians in 1941.

The diet, as reported herewith, was first employed in 1934. At that time the purpose of rotating and diversifying foods was not based upon the present concept of its functions, namely, to maintain tolerance or to prevent sensitizations from developing. It was prescribed with the idea of avoiding cumulative reactions. It was soon learned that cumulative reactions were not nearly so important as these two other factors. It became apparent that what, in most instances, was previously thought of as a cumulative reaction, was in reality, a recurrence of sensitizations.

With the development of this diet the next logical step was to employ it to *prevent the occurrence* of new sensitizations. The method was first used in 1935 for a patient who was subject to migraine of an extreme form. This patient reported, on history taking, that she had not been free of headache a single day during the past ten years. This history was confirmed during the first several months of study. The patient would show a few days' improvement whenever placed on a compatible diet as determined by individual food tests. Then, within a matter of five to ten days, her symptoms would return to their previous intensity. She was then given a general diet, except for three foods. Every food used was rotated and diversified so that each food was repeated at a specified interval. Various types of foods were used to secure the basic dietary requirements. The details of this case and the end results have been fully covered in another paper.⁵ Since that time (1935), the method has been studied in a large series of patients. Dr. Carroll Pounders began using this procedure in June, 1936 as a means of avoiding the development of new food allergies in his pediatric cases. It has also been used by Drs. Zeller, Leney, McNeill, Jackson, and Stoesser. Its value, in their hands, warrants the exposition of this method for general usage.

II. SELECTION OF FOODS FOR ROTARY AND DIVERSIFIED DIET

In selecting foods to be used for this diet, only those for which the patient has a tolerance are to be included. There will be many times when the status of tolerance cannot be ascertained accurately. However, one will *do the best possible* in the early stages of care, if *every food known* to be a cause of symptoms is omitted. There are certain general rules concerning food allergies that will be of value in selecting foods. It has been found that if a patient is sensitive to wheat, it is very easy to become sensitive to other members of the cereal family. If one is sensitive to one of the ripe legumes, it is often true that all members will cause symptoms; therefore these are best omitted until checked.

It has been found important to limit the use of certain foods at all times. Thus, if one can take buckwheat it is generally used at intervals, because past experience has indicated that most people become allergic to buckwheat if it is used regularly. If one is sensitive to wheat, then oats, rice, and corn are used at intervals until tests indicate other usage is feasible. It is very likely that corn will cause symptoms if it is used constantly by a wheat-sensitive person. There are, of course, exceptions to this rule.

If one is to select foods for which the patient has a tolerance, it is imperative that one has a command of the nature and changes which are characteristic of food allergy. Many of the failures in using dietary regimes are due to the fact that the user is not as well informed on the basic nature of food sensitizations as he is on the details of the diet he is using. Tolerance is, at all times, a relative thing; it merely implies that the patient has *no demonstrable symptoms, under the conditions* existing at the time of the specific test.

The frequency of use of selected foods will vary according to the conditions existing in each case. The factors to be considered are: (1) whether the food has ever been a cause of symptoms; (2) if the patient has a high or

low inherent tolerance to foods in general. Each of these two points will be considered more fully under the discussion concerning the use of the diet.

The number of feedings per day is *extremely important*. It is one normal serving at any selected meal. Thus, the rotary-diversified diet may be summarized as: a diet consisting of foods for which the patient *has a tolerance*, which will include *various types* of food necessary for a well-balanced diet. These foods are used at *intervals of two to seven days*, taking one normal serving per day at *one meal only*. Finally, it is used either to preserve tolerance, which has been acquired by omission of this food, or it may be used to prevent the initial development of food allergies, in known allergic individuals.

The use of the diet is to be guided by two cardinal facts:

1. *Its use to maintain tolerance.* This will include foods which previously have been proved to be a cause of specific symptoms but which can be used at present because tolerance has been gained by omission of the food.

2. *Its use to prevent the development of new allergies.* This will be the case, for the most part, in young patients. It is also used for adults, particularly those with low inherent tolerance.

III. USE OF THE DIET TO PRESERVE TOLERANCE

In adults this will be the most common cause for employing this procedure, although there will be a certain number of instances when it is used to avoid developing sensitizations.

Whenever a patient is proved sensitive to a food, it is omitted until tolerance develops, which is the case in the majority of sensitizations. This is a matter of three to eighteen months, varying with the patient and the syndrome. The food is checked for the first time at six months, then retested at nine months, if symptoms followed the first test. Another test is made at the end of the year; if there is still a reaction, the final test is made at eighteen months. If this test is followed by symptoms, it is best to consider the food as a permanent or fixed food allergy and discard it. At whatever test time the food fails to produce symptoms, the rotary principle of use is then applied. For six feedings it is used once daily, at five-day intervals. This is done so that if sensitization recurs, it will not mask itself. If no symptoms are induced by these six feedings, the patient is instructed to change the interval from five to three days. The food is used at this interval for three months. If still tolerated, the period may be reduced to once in two days.

There are very few foods which have been allergens that can be used after tolerance is achieved by elimination, at intervals of less than once in three days. There are such instances, however, and one may occasionally be able to reinstate a food to once daily, every day, without recurrence of active allergy. It is important to know that when a food is used once in seventy-two hours, the patient may become sensitive to it again and develop a complete masking of this allergy. Such recurrences of sensitization are insidious and progressive, as a rule. Therefore, in the course of using the diet, if the patient has an increase of symptoms, consider and evaluate the probability of the allergy recurring. If this be true, elimination must be used again, and when the food is compatible the next time the interval of usage must be doubled,

at least. Thus, if one becomes sensitive to wheat after using it three weeks at three-day intervals on the first trial, the second time it is used the interval should be six days. It is usually necessary to make a reduction of at least 50 per cent in the incidence of use, to be effective.

In the fourteen years since food sensitization was based on *demonstrable effect*, instead of upon a skin test reaction, I have not found any food which, after tolerance had been obtained, could be replaced in the diet and used with the same frequency as before the sensitization was proved, without the allergy recurring. Thus one might say, once allergic to wheat, always allergic to wheat, if the incidence of use is the same. There may be exceptions to this, *but it has not been proved*, whereas, the statement just made has been proved many times. It has been observed in patients with eczema that a food causing eczema in the baby does not necessarily cause asthma in childhood when the patient has become asthmatic. But, when a given food causes asthma at one time for this patient, it will do so as a rule, as long as the incidence returns to the old frequency. In using feedings of this type, I have been able to control symptoms of known allergens for eleven years. Then, during war-time restrictions the patient broke interval usage for two weeks and developed an active sensitization which has not subsided with six months' elimination.

If recurrence of sensitization is suspected, eliminate and re-test the food in the regular manner.

IV. USE OF THE DIET TO PREVENT THE DEVELOPMENT OF ALLERGIES

In this case the purpose in using the diet is to forestall the occurrence of an allergy. It will be used in two groups of patients, (1) the pediatric group and (2) adults. There are only superficial differences in these two groups, but with the adults many factors must be considered other than the diet, hence both usages will be delineated. Whenever a physician encounters allergy in an infant or a very young person, particularly if there are multiple allergies, it is wise to teach the patient to use this diet *as a prophylactic measure*. Since the interval use of various foods may be confusing to the mother or patient, I have devised a diet chart which makes it very easy for the cook, patient or mother, to determine the allowed foods for a given day or for days in advance. These diets are to be posted in the kitchen for ready reference.

As an illustration of the need and function of the rotary diversified diet, let us say that a one-year-old baby developed a rash which is proved to be due to oranges. Sneezing is produced by egg, and diarrhea by cod liver oil. Instead of substituting *one* fruit for the orange, have the patient use pineapple juice, *once daily, every third day*. Use prune juice in the same manner, and tomato or apple juice for the day following. Then it will be time to use the pineapple juice again. Thus, sources of vitamin "C" are diversified and rotated according to definite intervals. The patient is not sensitive to any of these rotated foods, nor is there any indication that he is about to become sensitive to them. The dietary procedure is carried out wholly to prevent the *probable occurrence of allergies*, since experience with other cases at this age indicate it is the rule, not the exception, for these patients to develop new allergies.

When new foods are added to the diet with time, these, too, may be rotated and the patient thus follows an eating pattern which gives him the advantage of using many foods, at the same time lessening to a very great degree the probability of developing sensitizations to them.

Pounders,³ who has used this diet since 1936, states that in his present pediatric practice there are not nearly as many allergies per patient in the present 10-to-12-year-old group dieted by this method as compared with the same age group whose allergies were treated by strict elimination and nonrotating substitution of one food for another.

It should be borne in mind that if a patient has become sensitive to a common food, say wheat, and one substitutes corn for wheat, it is entirely likely that the patient will also develop an allergy to corn. In fact, it is so true that I have emphasized that the physician's first duty to a wheat-sensitive patient is to determine the status of corn as regards tolerance or sensitization. A diet based on this principle has certain distinct advantages. It has a definite purpose: it is neither distasteful nor monotonous, nor short of necessary ingredients. In comparison to diets based on eating fancies and routine, it has much to offer the allergic patient.

The second group of patients in which this diet may be used are those in whom there are a number of definitely established allergies which have existed over a period of time. For the most part, these will be teen-age children and adults. The need for the use of this type of therapeutic measure will be governed by the patient's inherent tolerance to food. This is an inherent ability which varies with the patient, and determines the ratio between the incidence of a food in the diet and the development of an allergic status.

Thus, one patient may be able to eat a given food three times daily for five years, before it becomes a cause of allergy. Another person, whose apparent degree of sensitization and severity of symptoms are identical, may develop an allergy to any food which is used three times daily for ten days, or even less. Just what this factor is, has not been evaluated at present. Nonetheless, it is of extreme importance from the clinical standpoint. It means that certain patients can be treated by a narrowing, limited diet. In these patients it is satisfactory to eliminate the known allergens, paying little attention to what substitutions are used. One may safely use a very limited diagnostic diet for these patients, for they have a factor which I have called a *high inherent tolerance* for foods (narrow base of sensitization).

In contradistinction to this type of case there are the patients whose diet cannot be restricted to a few foods, in whom elimination diets for diagnosis are not effective and often increase symptoms after being used a few days or a week. They are, as a rule, patients whose symptoms have shown little improvement by customary plans of treatment; they are pale and often have moderate anemia without an abnormal blood cell picture. This group of patients I have labelled as having a *low inherent tolerance* for foods. They tend to become sensitive to any food which appears in their diet daily. In one such case, studied in 1934, only five foods did not produce a definite increase of

asthmatic symptoms. When the patient was placed upon this diet, improvement occurred on the fifth day, but by the eighth day symptoms were as severe as before. Re-tests of these five foods produced definite symptoms following ingestion of each. The patient was then gradually placed upon a rotary diet. Foods were added when elimination had produced tolerance, until finally the patient was eating all foods at intervals of two days and most of them were used at three-day intervals. When the diet was started, the patient required between eleven to thirteen injections of epinephrine daily. After the diet was fully established, and without any other changes in inhalant therapy or living conditions, only six injections of epinephrine were needed in forty-four consecutive months, four of these on one day. The patient then confessed to the use of pork two or three times daily, for the week preceding the use of these doses of epinephrine. Pork produced symptoms on deliberate, individual food testing.

It is not suggested here that every patient with severe symptoms has such reactions from food allergy. Experience will indicate to the careful observer in which patients diet is a probable factor, and then no changes should be made in the diet until the inhalants are treated and brought under control, or the diet should apply on a prophylactic basis until such studies are complete. Then individual food testing and continuance of the diet should proceed as indicated. It must be emphasized again that one never knows the effect of foods until they are properly tested. The statement from the patient that he knows certain foods are *not a cause of symptoms, is valueless*.

Again, one should keep in mind that this is not a diagnostic diet, since foods used at intervals of three days or less can mask themselves. However, if one feeds all foods at intervals of five days or more, masking will not occur. The purpose of this diet is not to diagnose, but to preserve tolerance and to prevent the development of sensitizations. Diagnosis will be more efficient if carried out by means of individual food testing.

The use of the rotary diversified diet can best be exemplified by case reports. It should be borne in mind that the diet is used for several reasons. First, it is employed to prevent the development of new sensitizations in patients with a low inherent tolerance or a broad base of sensitization. These patients are invariably difficult ones to handle and it is imperative that one should avoid producing new sensitizations to be added to the old ones. Second, the diet is used to preserve tolerance which has been acquired by prolonged and complete omission of a known allergic food. Finally, it is of most value as a prophylactic measure in allergic children. Each of these uses are illustrated from actual case records herewith.

CASE 1.—F. H., aged 35, was seen because of constant headaches of the so-called migraine type. In the course of making the diagnostic survey on foods, it was found, after seven months' trial, that it was impossible to keep this patient on any elimination diet and free her of symptoms. This was due to the fact that additions to the diet would provoke symptoms by the time that these foods were used long enough to establish freedom of symptoms, with the elimination of her active pre-diet sensitizations. Accordingly, it was decided to employ the rotary diversified diet as a means of preventing these rapidly developing allergies. The procedure was as follows: Each food was tested individually, and

if it provoked neither headache nor fatigue, it was added to the diet to be used once daily every other or every third day, the interval chosen being determined by the frequency of use previous to testing. Foods taken at least daily were continued once daily every other day. Foods taken at intervals of three days or longer were used not to exceed once in three days. One food, wheat, was eaten once daily without difficulty.

There were a number of foods, specifically milk, beef, and corn, which could not be taken in any amounts at any time without producing symptoms, and they were eliminated.

The effect of the diet was not fully established for a period of several months; a point which emphasizes the time requirements for establishing diagnosis and, in turn, relief, in the allergic patient.

In this particular individual there were no breakdowns in tolerance for foods used at intervals as indicated. This should be looked upon as an unusual feature rather than the expected course in this type of patient. It is very frequently the case that sensitizations will develop when foods are shifted from once weekly or a ten day interval to once every three days.

CASE 2—E P H, aged 35, came because of chronic nasal symptoms of itching, watering, sneezing, and congestion. These were practically constant for the previous ten years. In the course of diagnosis and treatment, it became necessary to eliminate one food after another due to constantly recurring symptoms which were due to foods which had been placed in the diet and used constantly upon the elimination of a previously existing sensitization. This method of treatment was carried out until the patient was restricted to five foods which of necessity had to be used at least once daily and for the most part, thrice daily.

At that time it was my opinion that the recurrence of symptoms after assigning a food to this patient's diet for three or four days' use was evidence of a cumulative type of sensitization. Accordingly, in order to avoid cumulative reactions, these foods were added and, if they did not provoke symptoms, were repeated at intervals of once in three days. This period was chosen because it had been observed so frequently that reactions continued after individual tests for fifty four to seventy two hours. It was assumed that the interval chosen would avoid a cumulative reaction. Actually, it was learned in the course of time that this procedure avoided the re-creation of old sensitizations, in other words, it preserved tolerance.

With this concept in mind, a systematic program was begun which consisted of testing foods which at one time had been eliminated because they produced symptoms. These foods were admitted to the diet and used once daily at five day intervals for six times, after which, if no ill effects were observed, the interval was changed to once daily every third day. Over a period of approximately nine months' time, it was possible to re-enter all foods save three at intervals of forty eight or seventy two hours. Two foods, wheat and corn, could not be used in this manner. Corn was not usable at all except in the green form (not a rare fact), wheat had to be eliminated strictly for four years and then could only be used once in five days without postdigestive symptoms.

It may be questioned if a rotation of foods with single usage in the day is not a problem of considerable magnitude in the average home. The writer, having used such a procedure for years, is of the opinion that it is no more difficult than any other diet when it has been used long enough to become established. Furthermore, there is no monotony such as occurs in many present-day diets.

This diet can be followed easily by the use of the chart (see Chart I). For example: beef is assigned to Monday and Thursday, chicken on Sunday and Wednesday, lamb on Tuesday, salmon on Friday, and pork on Saturday. Orange juice, instead of being a monotonous dietary habit to start each breakfast, becomes a refreshing introduction to breakfast on Sunday and Wednesday, while

prune juice is used on Monday and Thursday, pineapple juice on Tuesday and Friday, and apple, tomato, or grape² juice for Saturday. Other fruits are used in the course of each day, assuring the patient at least two good servings of fruit daily. This diet has produced eminently successful clinical results in a period of many years' time for this patient, and has been the only means of control which has proved practical, and after once being established, was self-managed, requiring only occasional suggestions and guidance.

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY

[illegible]

Chart 1. Chart for Rotary Diversified Diet.

CASE 3.—B. S., aged 6, was seen because of eczema of several years' duration. She had been treated previously, and in the course of allergic management, had been placed upon a so called diagnostic diet consisting of six foods. She had grown worse upon this diet and sought assistance because of the presumably incurable allergic problem.

It was discovered that three of these six foods were actually the cause of symptoms, and upon their elimination, clinical cure was effected.

In the course of discussing her problem, that is, eczema and the subsequent clinical course of the average allergic child, the mother expressed concern over what she might do to prevent the occurrence of asthma in the distant future and a recurrence of eczema in the near future. It was explained to her how to avoid certain inhalants such as excessive house dust, and how to avoid feathers, orris root, and massive pollen doses.

In the handling of the diet, the mother was advised to practice a rotation and diversification of the diet, not because her daughter was sensitive to these foods, but to avoid sensitization, since it had already been established that the child became allergic with great ease.

Subsequent observation has established the fact that eight years later this child is not restricted on a single food and has remained free of all allergic manifestations since following this diet.

It may well be argued that it is futile to practice means of avoiding the development of asthma in an eczematous individual. Occasional success with such patients could easily be the result of factors other than adherence to the diet. However, our experience and that of pediatricians who have used this procedure for over ten years has led to the observation that the incidence of food allergy in groups of children on whom rotation and diversification were practiced is but a small fraction of the incidence in a similar age and economic group where such measures were not used. Our combined experience is sufficient to state without equivocation that the method is of distinct value when correctly carried out.

SUMMARY

The nature, use, and indications of the rotary-diversified diet have been made. The nature of the diet is to use *one normal serving* of various selected foods, once daily, at intervals of two to seven days.

The diet is to consist of foods for which the patient has a tolerance, that is, foods which are not capable of provoking allergic symptoms.

The diet may be used to maintain tolerance for foods which have previously caused symptoms, but have become compatible by avoidance for a period of time.

The diet may also be used prophylactically to prevent the development of new allergies. This is of especial value for infants and young children but may be used at all ages.

The indications for its use are rapidly developing allergies when substitutions are made, and low inherent tolerance to foods. The diet should not be used as a substitute for diagnosis.

Since foods used at intervals, as suggested in this diet, may develop an insidious recurrence of sensitization and mask themselves perfectly, this possibility must be evaluated when suspected.

Finally, there is only one method to ascertain the effect of a food, *individual deliberate* test. When the diet is apparently failing to produce the desired results, testing is indicated.

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PHYSICAL GROWTH OF CHINESE INFANTS

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DURING the years 1935 to 1940, the writer accumulated physical growth data on "well-nourished" Chinese babies extending over the first postnatal year. It is the purpose of this paper to communicate the results from analysis of these data.

SOURCE AND SELECTION OF SAMPLE

The data were collected at three institutions, each maintaining a maternity nursery and a well-baby clinic: Margaret Williamson's Hospital in Shanghai (1935); West China Associated University Hospital in Chengtu (1937); and St. Elizabeth Hospital in Shanghai (1940-41).

Not all available infants were included in the study. The writer subjected each available infant to a medical examination and estimated its general nutritional status. A four-category classification was used: +++ ("clinically healthy"), ++, +, and \div ("malnourished"). Infants falling in the last two categories were rejected. The subjects on which the study is based were selected accordingly. They were rated either as "clinically healthy" (+++) or only "moderately flabby" (++) .

MEASUREMENTS TAKEN

Records were obtained for body weight, stem (vertex-rump) length, and total (vertex-heels) length. Weight was taken nude, on a balance accurate to within 10 Gm. The length measurements were likewise determined with the babies lying nude. The instrument employed was a sliding calipers (a long ruler with two transverse bars, one fixed to the end of the ruler and the other movable). The procedure in measuring total length was as follows: The baby was laid with its long axis paralleling that of the ruler; an assistant held both its feet with one hand, pressed upon both knees with the other, and checked that the heels were brought into contact with the fixed bar; the writer held the infant's head by its jaw and moved the sliding bar of the instrument into contact with the vertex. The procedure in determining stem length was the same, except that the assistant elevated the infant's thighs and pressed the buttocks into contact with the fixed bar of the instrument.

FINDINGS AT BIRTH

The body size of "well-nourished" Chinese infants at birth was studied, utilizing data collected at St. Elizabeth Hospital. Table I presents the major results from analysis of these data. Weight was taken shortly after birth and the other measurements within the first twenty-four postnatal hours. For each measurement the means are slightly larger on the male infants than on the female infants. Fifty per cent of the male infants had birth weights between

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2.84 kg. and 3.25 kg.: the central one-half of the female birth weights fell between 2.82 kg. and 3.24 kg. Average stem length (vertex-rump) in this sample of Chinese neonates will be seen to approximate 68 per cent of average stature (vertex-heels).

TABLE I. THE BODY SIZE OF NUTRITIONALLY SELECTED CHINESE INFANTS STUDIED IN SHANGHAI (1940-1941)

	N	MEAN	MINIMUM	PERCENTILES			
				25	50	75	MAXIMUM
Males							
Weight (kg.)	118	3.23	2.5	2.84	3.08	3.25	4.0
Vertex-heels (cm.)	116	49.3	43	48.2	49.2	50.2	53
Vertex-rump (cm.)	118	33.6	28	32.7	33.5	34.3	37
Females							
Weight (kg.)	110	3.18	2.5	2.82	3.03	3.24	3.8
Vertex-heels (cm.)	114	49.0	43	48.0	48.8	49.9	53
Vertex-rump (cm.)	112	33.0	28	32.4	33.2	34.0	36

GROWTH IN WEIGHT DURING FIRST POSTNATAL WEEK

The trend of the weight curve in Chinese infants over the first week of postnatal life was studied on material collected at the St. Elizabeth Hospital. Use was made of approximately 100 subjects of each sex. Mean weight was computed on the full samples at birth and on decreasing portions of each sample at successive days following birth. Table II displays the findings. It will be seen that for both sexes there is a loss in mean weight over the first two postnatal days. The loss approximates 200 Gm., or 6 per cent, on the male infants and 170 Gm., or 5 per cent, on female infants. Between two and seven postnatal days there is registered a slight over-all trend of increase in weight.

TABLE II. MEAN WEIGHT (KG.) OF NUTRITIONALLY SELECTED CHINESE INFANTS AT SUCCESSIVE DAYS DURING THE FIRST POSTNATAL WEEK

AGE (DAYS)	MALES		FEMALES	
	N	MEAN	MEAN	N
Birth	102	3.23	96	3.18
1	74	3.12	71	3.07
2	70	3.03	66	3.01
3	52	3.08	69	3.01
4	73	3.10	64	3.04
5	71	3.09	61	3.04
6	58	3.10	50	3.05
7	35	3.07	29	3.10

GROWTH IN WEIGHT, STATURE, AND STEM LENGTH FROM 2 TO 50 WEEKS OF AGE

In studying the physical growth of Chinese infants between the first and twelfth postnatal month, records were combined from St. Elizabeth Hospital, West China Associated University Hospital, and Margaret Williamson's Hospital. It will be recalled that one of these hospitals is located in Chengtu and the other two in Shanghai.

The records were separated for analysis by sex, measurement, and month of age. This resulted in 72 subgroups, twelve age subdivisions for each of the three measurements on each sex. Table III lists the central tendency value

(mean) of every subgroup. Inspection of Table III shows that in general Chinese male children exceed Chinese female children throughout the first postnatal year in average weight, stature, and stem length.

TABLE III. THE BODY SIZE OF NUTRITIONALLY SELECTED CHINESE INFANTS STUDIED IN SHANGHAI AND CHENG TU (1935-1941)

AGE (MO.)	NO. INFANTS	WEIGHT MEAN (KG.)	VERTEX-HEELS MEAN (CM.)	VERTEX-RUMP MEAN (CM.)
<i>Males</i>				
0.5	77	3.75	52.6	35.3
1.5	202	4.76	55.7	37.5
2.5	182	5.60	58.4	39.3
3.5	141	6.26	60.5	40.7
4.5	111	6.74	62.5	41.6
5.5	95	7.16	63.9	42.5
6.5	93	7.61	65.4	43.0
7.5	79	7.94	66.9	44.2
8.5	78	8.37	68.0	44.8
9.5	66	8.38	68.7	45.1
10.5	42	8.82	71.8	46.7
11.5	46	8.85	71.9	46.5
<i>Females</i>				
0.5	56	3.54	51.8	34.7
1.5	151	4.47	54.6	36.6
2.5	105	5.22	57.3	38.2
3.5	90	5.89	59.8	39.4
4.5	46	6.48	61.6	40.8
5.5	51	7.20	63.7	42.4
6.5	41	7.20	64.7	42.8
7.5	40	7.47	65.9	43.2
8.5	30	7.68	67.2	44.4
9.5	26	7.79	68.2	44.5
10.5	20	8.67	70.9	46.3
11.5	18	8.82	72.3	46.8

TABLE IV

AGE PERIOD (MO.)	WEIGHT (KG.)		VERTEX-HEELS (CM.)		VERTEX-RUMP (CM.)	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0.5-3.5	2.51	2.35	7.9	8.0	5.4	4.7
3.5-6.5	1.35	1.31	4.9	4.9	2.3	3.4
6.5-9.5	0.77	0.59	3.3	3.5	2.1	1.7

Changes in the rate of growth of Chinese infants during the first year may be conveniently indicated by calculating the differences between equally spaced means. Differences between means from Table III representing ages three months apart are reproduced in Table IV.

For each of the three measurements there is registered a declining rate of growth with age. Note that the increase in the mean from 0.5 to 3.5 months is greater than that from 6.5 to 9.5 months by approximately 1.75 kg. for weight, 4.5 cm. for stature, and 3.1 cm. for stem length.

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SUBLUXATION OF THE HEAD OF THE RADIUS "NURSEMAID'S ELBOW"

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REPORTS of subluxation of the head of the radius, commonly called "nursemaid's elbow," are ubiquitous in the literature. Mention of it has been found as far back as in the writings of Hippocrates, but it was first accurately described by Fournier¹ in 1671. During the nineteenth century it was a favorite subject among the French and German writers. Though Gardner² wrote of it in 1837, Poinso³ in 1885, Moore⁴ and Cushing⁵ in 1886, and Van Santvoordt⁶ in 1887, the "granddaddy" of the American articles was by Van Arsdales⁷ in 1889, when he reported 100 cases and presented a thorough discussion. Since that time there have been sporadic accounts of the subject, nearly all of which have been in foreign literature. The latest article in American literature was by Anderson⁸ in 1942.

The purpose of this paper is not to report an unusual occurrence, but rather to emphasize the frequency with which subluxation of the head of the radius occurs and to stress the fact that, although it is a situation involving bone and joints, it is a pediatric problem and should be treated by the pediatricist.

The word "luxation" means dislocation; subluxation, therefore, refers to partial or incomplete dislocation. Subluxation of the head of the radius is limited to children, and usually very young children, when they are most likely to be still under the care of a child specialist. The youngest reported case was a 3-month-old infant and the oldest was a 9-year-old child. By referral and conversation it has been learned that orthopedists generally are not familiar with subluxation of the head of the radius and, therefore, incur much unnecessary expense and trouble in its diagnosis and treatment. However, the subject is slighted by pediatric textbooks and only scattered few orthopedic texts briefly mention it.

The condition has been given a variety of names, including Gromyer's injury, dislocation of the head of the radius by elongation, dislocation of the head of the radius downward, and, our own favorite, nursemaid's elbow. The manner in which the injury is sustained is almost identical in every instance; that is, a sudden pull on the extended arm of a small child. Picking up a child by one arm after a fall, pulling a child from under a table, helping a child across the street and up the curb, or when one child pulls a toy from another child are all common examples of a quick pulling motion on the outstretched arm. Occasionally the condition is sustained in a fall, in which case the history may be misleading.

A typical case history is as follows:

W. J., a 3-year-old boy, was being led by the hand from one room to another by his nursemaid when he stumbled. In an effort to prevent him from falling the nursemaid quickly

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jerked his hand upward. The boy immediately cried out in pain and, upon being released, sat on the floor and refused to use the arm. He continued to cry and resisted any effort at assistance. When the pediatrician (who was called) arrived, the child was found still sitting on the floor with his left arm hanging by his side, the elbow slightly flexed so that the forearm and hand rested on his lap; the hand was in the position of pronation. The child was too tearful to be of much assistance, but it was determined that the main point of pain was at the wrist, which he fondled gently with his right hand. On examination, however, there was no limitation of motion at the wrist joint and no tenderness. On further examination it was found that there *was* tenderness over the head of the radius and, although flexion and extension of the elbow joint was accomplished, there was encountered definite resistance on attempting to supinate the hand, the effort being accompanied by a scream of pain from the child. The diagnosis of subluxation of the head of the radius was made by the physician and reduction was effected, attended by the characteristic click.

This case illustrates several important points. (1) The history of the manner in which the injury was sustained is most important and leads one to think immediately of subluxation of the head of the radius. If history is unobtainable, as is often the case when children are hurt at play, it is wise to rule out fractures and dislocations first in order to avoid doing further injury. (2) The position of the arm is characteristic. It hangs limply by the side with the elbow flexed at about 20 degrees and the hand in pronation. (3) Pain may be limited to the elbow, but more frequently it is referred to the wrist. The reason for this has never been explained adequately; some writers state that it is due to the stretching of a nerve, others say it is due to the pinching of a nerve. Though how either can occur with the injury we cannot discern. (4) There is a point of acute tenderness over the head of the radius. (5) All motions of the arm and hand can be carried out with the exception of supination. Attempts at supination meet with an abrupt obstruction about midway and the child experiences severe pain. (6) No deformity can be demonstrated externally and the x-ray reveals no abnormality. Stone⁹ states that if roentgenograms of both elbows are made there can be measured a greater distance from the head of the radius to the capitulum of the humerus on the affected side than on the unaffected side. Others refute this claim and roentgenologists agree that the difference is so slight that unless the condition was looked for specifically it would not, in all probability, be discovered. (7) The click heard or felt when reduction is accomplished is disputed by no one. This click in itself is assurance that the diagnosis was correct and that the treatment has been successful. Without it one cannot be sure of reduction. However, if manipulation is not followed by a click the arm may be placed in a sling and autocorrection will occur in one to two days. To illustrate this point we cite the following case.

A. S., a 4-year-old boy, was being led by the hand across a busy street by his mother and assistance was given the child in mounting the curb by lifting on the arm. The child immediately cried out with pain and refused to use the arm. A physician's office was located in the block and the child was taken there. Examination failed to enlighten the physician and the child was sent to the office of an orthopedist, who took an x-ray of the affected arm. The x-ray was interpreted as being negative. On being unable to arrive at a definite diagnosis, the orthopedist placed the child's arm in a sling and asked that he return for further examination in two days. On returning the arm was being used normally and the mother stated that she noticed it normal just that morning when the child awoke, it having been carried in the sling entirely the previous day.

Undoubtedly this was an instance of subluxation of the head of the radius. Immediate reduction was not accomplished, but when the arm was placed in a sling autoreduction occurred and the child had no further trouble.

Protean theories have been propounded to explain the pathology of subluxation of the head of the radius, but as these cases are never fatal, autopsy findings are lacking. Slight anterior or posterior displacement of the head of the radius, the locking of the tuberosity of the radius below the edge of the ulna, and the interposition of soft parts between the two bones have all been suggested and disproved. The most likely theory and the one with the most support was set forth by Stone⁹ in 1916 following a number of experiments on twelve arms from the anatomy laboratory. He showed that with hyperextension and pronation the annular ligament of the elbow joint was allowed to slip over the head of the radius into the space between the head of the radius and the capitulum of the humerus. Prior to the age of 7 years the head of the radius and the shaft of the radius are of practically the same diameter,¹⁰ allowing easy passage for the head of the radius through the annular ligament without laceration. If laceration of the ligament occurred there would be edema and induration of the joint for several days, which is not the case. Also, it is between the ages of 2 and 5 that the child is walking around with frequent lifts by the hand from taller individuals, thus making the highest incidence of subluxation at this age.

The incidence of occurrence was stated by Van Arsdale to be one per cent of surgical cases in children under 9 years of age. No other report of a sufficiently large number of cases has been made to change this figure.

Recurrences are not uncommon, especially in those children of frail stature and poor musculature.

There are no sequelae incident to its occurrence or correction.

The proper manipulation for correction and reduction of the subluxation is simple. The elbow is flexed to about 90 degrees and one thumb of the operator is placed over the head of the radius, exerting moderate pressure upon it. The patient's hand and forearm is then forcibly supinated beyond the point of obstruction. If the operation has been successful the characteristic click can be heard or felt and the child will begin to use the arm. If the subluxation has been standing overnight there will be some edema of the elbow joint and the child will not use the arm immediately in spite of reduction. It is best to place the arm at rest in a sling for a day or two in cases of this sort.

SUMMARY

The subject of subluxation of the head of the radius has been presented again to stress the frequency with which it occurs and to bring out the fact that, because of its limitation to small children, it is a pediatric problem and should be treated by the pediatrician. The diagnosis is made on (1) the suggestion of the history, (2) the lack of deformity at the site of injury, (3) point tenderness over the head of the radius, and (4) the loss of function and the typical position of the extremity. Treatment consists of moderate pressure over the

head of the radius with forceful supination of the hand. Successful treatment is accompanied by the characteristic click.

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BLOOD CHEMICAL AND IMMUNOLOGIC EFFECTS OF ADRENAL CORTICAL EXTRACT IN CHILDREN

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IN EXPERIMENTAL animals, a single injection of pituitary adrenotrophic hormone or adrenal cortical extract causes a decrease in total leucocyte count, a decrease in the absolute number of lymphocytes, an increase in the absolute number of polymorphonuclear leucocytes, and an initial increase in hemoglobin and erythrocyte count.^{1, 2} These changes are evident three hours after the injection. They are maximum nine hours after the injection in the case of pituitary adrenotrophic hormone and six hours after the injection in the case of adrenal cortical extract. Adrenalectomy, on the other hand, causes a trend toward anemia, absolute lymphocytosis, and decreased polymorphonuclear leucocyte production.²

Lymphocytes of normal rabbits have been shown to contain a protein fraction identical with the gamma globulin of the serum.³ It has also been recently demonstrated that antibodies are concentrated in lymphocytes.^{4, 5} Marked anamnestic response of agglutinin titers to washed sheep erythrocytes has been demonstrated to be produced by injection of adrenal cortical extract or adrenotrophic hormone in mice previously immunized to washed sheep erythrocytes following the lapse of a sufficient interval of time to allow these titers to fall to zero.⁶ A similar phenomenon was demonstrated in rabbits.⁷ Coincident with this and with the development of lymphopenia there has also been demonstrated a small but significant increase in serum proteins.⁸ This increase is in the globulin fraction.³

Injection of adrenal cortical extract causes hypercholesterolemia in rabbits.⁹

In adrenalectomized animals, none of these changes occur following the injection of pituitary adrenotrophic hormone, but they do occur following the injection of adrenal cortical extract.

It was felt that it would be interesting to determine if doses of adrenal cortical extract of reasonable size for clinical use would produce similar effects in human subjects.

MATERIALS AND METHODS

The studies reported were carried out on six children, 3 to 14 years of age, four of whom were hospitalized for fractures and two for physiotherapy treatment for postpoliomyelitis paralysis. These patients were all bedridden throughout the experiment. None of them showed any evidence of glandular disturbance or malfunction of any type.

Each child was given an injection of 1 c.c. of pertussis vaccine (40,000 million per cubic centimeter)* on each of two occasions, two weeks and one week before the beginning of the experiment.

From the Department of Pediatrics, University of Minnesota.

*Produced by Cutter Laboratories, Berkeley, Calif.

On the days of the experiment the children were allowed the regular hospital dinner at 11:30 A.M., blood samples were drawn at 3 P.M., a standard meal consisting of five soda crackers and a pint of milk was given at 5:30 P.M., and blood samples were drawn again at 9 P.M. On the first experimental day subjects 1, 3, and 5 were given an injection of 5 c.c. of adrenal cortical extract† immediately following the withdrawal of the first blood sample at 3 P.M. Subjects 2, 4, and 6 were used as controls. One week later the experiment was repeated with subjects 1, 3, and 5 being used as controls and subjects 2, 4, and 6 being used as experimental subjects, each receiving an injection of 8½ c.c. of adrenal cortical extract immediately after the withdrawal of the 3 P.M. blood sample. Thus, blood samples were drawn from the experimental subjects immediately before the injection of adrenal cortical extract and six hours after its injection, and blood samples were drawn from the control subjects at corresponding times. In this way each subject was used once as an experimental subject and once as a control subject. The data could thus be paired in such a way that each subject served as a control for himself as an experimental subject.

On each of the blood specimens drawn the following determinations were done: hemoglobin, erythrocyte count, leucocyte count and differential, sedimentation rate (read at 20, 40, 60, and 80 minutes), blood glucose, serum cholesterol, total and fractional protein, and pertussis titer. On each day a Tiselius electrophoretic pattern was obtained on the pooled serum of the three experimental subjects both before the injection of adrenal cortical extract and six hours after its injection. All hematologic determinations were carried out by the same graduate technician using the standard methods routinely employed by the University of Minnesota Hospitals. Pertussis titers were done by Dr. A. C. Kimball of the Minnesota Department of Health. Electrophoretic analyses were done by Dr. D. R. Briggs of the Division of Agricultural Biochemistry of the University of Minnesota. Blood chemistry determinations were done by one of us (V. C. K.) by standard micro methods.

For the electrophoretic studies, exactly 2 c.c. of serum from each of three subjects was pooled to give a total sample of 6 c.c. This pooled sample was dialyzed for three days at a temperature of 4° C. against a sodium veronal buffer of pH 8.6 and ionic strength of 0.1, the buffer being changed each day and the final dialysis being made against a volume of 3 L. of buffer. The serum specimen was then clarified by centrifugation and diluted to a total volume of 25 c.c. with the buffer against which the final dialysis had been made. This buffer was also used to fill the electrode chambers of the electrophoresis cell. The electrophoretic patterns of these diluted sera were then obtained after 7,500 seconds of electrophoresis under a potential gradient of 7.03 volts per centimeter by the "schlieren scanning" method of Longworth.¹⁹

Blood pressure, pulse, respirations, and temperature were recorded at hourly intervals throughout the experiment.

RESULTS

The results of the cholesterol and sugar determinations are shown in Table 1. The data are paired such that the values obtained for each subject on the

¹⁹Produced by the Upjohn Company, Kalamazoo, Mich.

day he was used as a control and on the day he was used as an experimental subject are shown side by side. As will be noted from the table, the cholesterol level at 9 P.M. was lower than that at 3 P.M. in all cases in which no adrenal cortical extract was injected and higher in all cases in which adrenal cortical extract was injected. Thus the injection of adrenal cortical extract apparently caused an increase of the cholesterol level in all cases. Analysis of the data on the sugar determinations in the same manner reveals that the effect of injection of adrenal cortical extract was a decrease in the blood sugar concentration in five of the six cases.

Similar analysis of the data on hemoglobin, erythrocyte counts, leucocyte counts, differential counts, sedimentation rates, total protein, albumin, and albumin-globulin ratios revealed no consistent changes in either direction.

TABLE I. EFFECT OF INJECTION OF ADRENAL CORTICAL EXTRACT ON CHOLESTEROL AND GLUCOSE LEVELS

SUBJECT NO.	TIME (P.M.)	GLUCOSE (MG. %)		CHOLESTEROL (MG. %)	
		CONTROL ¹	EXPERIMENTAL*	CONTROL ¹	EXPERIMENTAL*
1	3	131	109	165	140
	9	106	78	155	155
	Difference	-25	-31	-10	+15
2	3	91	109	245	190
	9	93	93	220	190
	Difference	+2	-16	-25	0
3	3	96	80	87	110
	9	80	73	78	118
	Difference	-16	-7	-9	+8
4	3	72	105	197	155
	9	83	87	183	167
	Difference	+11	-18	-16	+12
5	3	83	107	218	172
	9	93	90	208	195
	Difference	+10	-17	-10	+23
6	3	65	91	165	172
	9	80	80	144	184
	Difference	+15	-11	-21	+12

*Figures in the columns designated "experimental" represent levels of glucose and cholesterol determined on blood drawn just before and six hours after the injection of adrenal cortical extract. In the column designated "control" are the levels determined on blood drawn at corresponding times of the day, but on these days no adrenal cortical extract was injected.

TABLE II. EFFECT OF INJECTION OF ADRENAL CORTICAL EXTRACT ON PERTUSSIS TITERS

SUBJECT NO.	TIME (P.M.)	CONTROL DAYS*	EXPERIMENTAL DAYS*
1	3	1-320	1-640
	9	1-640	1-640
2	3	1-640	1-1280
	9	1-640	1-1280
3	3	Neg.	Neg.
	9	Neg.	Neg.
4	3	1-1280	1-640
	9	1-640	1-320
5	3	Neg. (± 120)	Neg.
	9	Neg. (± 180)	Neg.
6	3	1-160	1-80
	9	1-160	1-80

*Figures in the column designated "experimental day" represent titers of blood drawn just before and six hours after the injection of adrenal cortical extract. In the column designated "control day" are the titers of blood specimens drawn at corresponding times but on these days no adrenal cortical extract was injected.

In Table II are presented the pertussis titers. It will be noted that there are no significant effects on these titers following the injection of adrenal cortical extract.

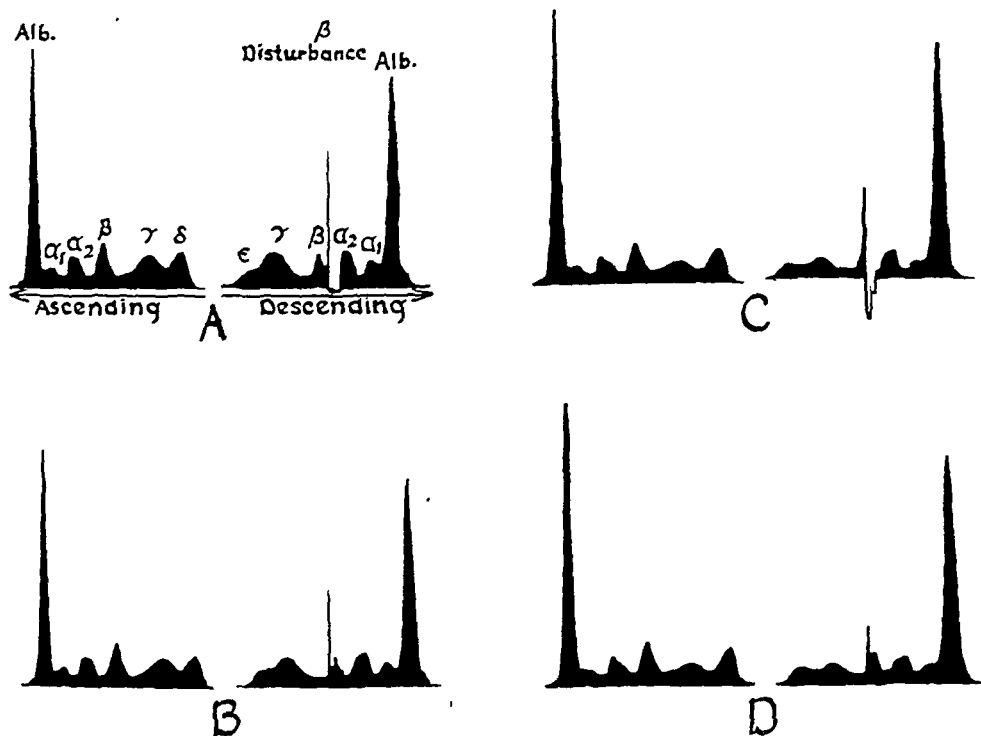


Fig. 1.—Electrophoretic patterns of pooled serum specimens drawn before and after the administration of adrenal cortical extract.

A, pattern of pooled serum of subjects 1, 3, and 5 before administration of adrenal cortical extract.

B, pattern of pooled serum of subjects 1, 3, and 5 six hours after administration of adrenal cortical extract.

C, pattern of pooled serum of subjects 2, 4, and 6 before administration of adrenal cortical extract.

D, pattern of pooled serum of subjects 2, 4, and 6 six hours after administration of adrenal cortical extract.

The electrophoretic patterns obtained from the pooled specimens of serum are shown in Fig. 1. It will be noted that the ascending patterns of corresponding serum specimens are virtually identical. Calculations of the proportions of the various electrophoretic components present did not reveal any significant differences between the samples drawn before the injection of adrenal cortical extract and those drawn six hours after its injection. However, in the case of the descending patterns there is an interesting difference in appearance between the patterns of sera drawn before the injection and six hours after the injection of adrenal cortical extract. In the former, the beta disturbance peak is located on the side of the beta-globulin peak toward the alpha globulin peak and in the latter on the side toward the gamma globulin peak.

There were no significant changes noted in blood pressure, respirations, pulse, or temperature during the course of these experiments.

DISCUSSION

The significance of the observation of a shift in the position of the beta-disturbance in the descending electrophoretic patterns following the injection of adrenal cortical extract is not apparent, but it may be mentioned in passing that we have previously noted the beta-disturbance in electrophoretic patterns of the sera of normal children to be in a position corresponding to that here found in the samples drawn previous to injection of adrenal cortical extract, whereas the type of curve obtained following the injection of adrenal cortical extract is the one commonly observed in electrophoretic patterns of sera of adults. There is evidence¹¹ that the beta disturbance is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha-globulin components of the serum (i.e., in the descending leg of the electrophoretic cell). It would appear that this lipoprotein complex is altered in such a way as to change its electrophoretic mobility under the influence of injected adrenal cortical extract. However, an exact interpretation of this phenomenon is not justified until a more conclusive proof of the precise nature of the normally occurring beta disturbance is forthcoming.

We have found no significant or consistent difference between hemoglobin, erythrocyte count, leucocyte count or differential, total lymphocyte count, total polymorphonuclear leucocyte count, sedimentation rate, total and fractional serum proteins, or pertussis titer determinations done immediately before and six hours after the injection of adrenal cortical extract. It has been suggested by Dougherty,¹² in agreement with our own conclusions, that the discrepancies between these findings and those previously reported on experimental animals might be explained on the basis of the fact that the doses of adrenal cortical extract injected in this experiment were considerably smaller in relation to the weight of the subjects than were the doses in the animal experiments. The doses used in this experiment were chosen because it was desired to determine the effects of clinically feasible amounts of material for injection. It would be desirable to repeat this study using amounts of adrenal cortical extract comparable, in terms of cubic centimeter per unit of the subject's body weight, to the amounts used in previous animal experiments. Such a study is contemplated.

SUMMARY

The data presented confirm in human subjects the finding of elevated cholesterol levels following the injection of adrenal cortical extract. They further suggest a tendency toward a lowering of the blood sugar level following the injection of this material.

A shift in the position of the beta disturbance in the descending electrophoretic patterns was observed in these same subjects.

A complete hemogram, sedimentation rate, total and fractional serum protein, and pertussis titer studies failed to show any significant changes.

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CONGENITAL HEMOLYTIC ICTERUS, FOUR GENERATIONS

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IN THE clinical study and treatment of two cases of familial hemolytic anemia or acholuric jaundice, a careful study of the histories, particularly the maternal histories, in four generations, was made, confirming the hereditary factor of the condition.

Campbell and Warner,¹ in their careful analyses of this subject, emphasized that the disease is inherited as a Mendelian characteristic, though there are no data to indicate the result to be anticipated from parental stigmata of the condition on both sides, as such a coincidence has not been reported, but this hereditary characteristic is transmitted to 50 per cent of the offspring of the first generation with subsequent hereditary dominant and recessive radicals.

The disease presents many varying degrees of clinical manifestations and as Weber² has demonstrated, the forms of the disease may be characterized by jaundice, anemia with no apparent jaundice (though adequate tests may show an increase in the serum bilirubin), splenomegaly, or the asymptomatic members of the family may only show increased fragility of the red blood cells.

Typically, a case of the disease would show a hypochromic, microcytic type of anemia, with reticulocytosis, increased red blood cell fragility, and with jaundice, splenomegaly, and fever. The finding of any one of these in a member of a family where the disease has been diagnosed marks this individual with a subclinical type of the disease.

The disease may first manifest itself in infancy or childhood, as in the congenital type, or in adults, in the latent type, and is frequently aggravated by acute illness.

CASE REPORTS

CASE 1.—B. S., an 8-year-old white girl of English-American parentage, in good nutritional status, was acutely ill with a chief complaint of nausea, vomiting, malaise, fever (104° F.) and yellowish skin. The maternal grandmother and a maternal aunt have histories of familial hemolytic anemia. There are two brothers, one living and well, and two sisters, one living and well. An aunt (maternal) had a splenectomy. Past history was negative. The patient first became ill on March 19, 1946, when she complained of anorexia, nausea, vomiting, and headache. She had a fever and a yellow tinge to the skin which grew progressively more pronounced. The mother noticed the yellowish tinge to skin and the similarity to the condition seen in the grandmother and aunt. Physical examination revealed a pale, thin child with a yellow tinge to the conjunctiva, a spleen palpably enlarged to within four fingerbreadths of the midline, three below the costal margin, and tender to pressure; all else was apparently normal.

Listed below are dates of transfusions, hemograms, and data obtained from laboratory reports:

March 22, 1946.—Hemoglobin was 40 per cent, red blood cells, 2,100,000; white blood cells, 6,100; polymorphonuclears 66 per cent, lymphocytes 31 per cent, monocytes 2 per cent and eosinophiles 1 per cent. Marked anisocytosis and moderate eccentric achromia were present, with many microcytes and few poikilocytes, and a few cells showing slight polychromatophilia. There was no basophilic stippling or nucleated red blood cells. There was a marked degree of anemia, of combined type, with definite leucopenia and relative increase in lymphocytes. The icterus index was 20. The Van den Bergh direct reaction was negative, indirect was 3.7 mg. per 100 c.c.

On March 23, 250 c.c. citrated blood were given. Hemoglobin was 21 per cent, red blood cells 1,320,000, white blood cells 4,800, polymorphonuclears 63 per cent, lymphocytes 35 per cent, monocytes 2 per cent. On March 25, 250 c.c. citrated blood were given. The stool examination was negative. Fragility at beginning hemolysis was 0.48 per cent and at complete hemolysis was 0.36 per cent. March 27 and 29, 250 c.c. citrated blood were given. On March 27, hemoglobin was 45 per cent, red blood cells 2,660,000, white blood cells 13,500, polymorphonuclears 78 per cent, lymphocytes 21 per cent, monocytes 1 per cent. On March 29, hemoglobin was 46 per cent, red blood cells 2,680,000, white blood cells 8,200, polymorphonuclears 75 per cent, lymphocytes 24 per cent, monocytes 1 per cent. Operation was on April 2, 1946. Citrated whole blood (250 c.c.) was given April 3, 4, 6, and 9. On April 3, hemoglobin was 50 per cent, red blood cells 2,750,000, white blood cells 8,800, polymorphonuclears 69 per cent, lymphocytes 30 per cent, monocytes 1 per cent. On April 4, hemoglobin was 68 per cent, red blood cells 3,530,000, white blood cells 15,700, polymorphonuclears 90 per cent, lymphocytes 6 per cent, monocytes 1 per cent, basophiles 3 per cent. On April 6 fragility at beginning hemolysis was 0.40 per cent and at complete hemolysis was 0.32 per cent. April 9 hemoglobin was 69 per cent and the red blood cells were 3,820,000.

Synopsis of Operative Procedure, April 2, 1946.—A subcostal incision was made parallel to the costal margin in the left upper quadrant, through which the abdomen was explored. The spleen was found to be about twice normal size. There were some adhesions to adjacent viscera at its upper extremity but not to the diaphragm. It was delivered through the incision after separating the adhesions, and was separated from its proximity to the stomach and pancreas. It was gently compressed to reduce its engorgement and the splenic artery was first ligated with #1 chromic sutures. The venous radicals were then ligated in like manner and there was no bleeding at the site of splenectomy. The appendix was then removed.

Pathologist's Report by Dr. Oscar B. Hunter.—Grossly, the spleen is covered by a slate gray capsule which is smooth, but the underlying splenic tissue is somewhat wrinkled. It is fairly firm and on section cuts with slightly increased resistance, revealing a red splenic pulp in which are found numerous tiny, grayish-white miliary lesions. No evidence of infarction, abscess, or other specific pathology is noted.

Microscopic Examination.—Sections from the spleen reveal considerable thickening of the capsule and a number of fibrous tissue trabeculae extending into the splenic pulp. The latter is completely filled with numerous red cells and the splenic corpuscles are compressed and have lost much of their typical appearance, although in some instances there is a remnant of the corpuscle present. The sinuses are almost completely devoid of contents. Throughout the spleen there are numerous areas showing some hemosiderin deposit, but a true marked hemosiderosis is not present. The vessels show some thickening of their walls in some areas and in a number of instances contain varying amounts of coagulated serum, typical of familial hemolytic icterus.

CASE 2.—This patient was a first cousin (maternal) of the first patient. The disease was diagnosed here as well.

S. G., a 5-year-old white girl of German-American parentage, had a chief complaint of fever (102.8° F.), anorexia, and running nose. The father was living and well; the mother had splenectomy for familial hemolytic anemia three years previously; the maternal grandmother and great-grandmother had anemia and jaundice, the maternal grandmother was still living; the patient had no brothers or sisters. Past history was negative except for constipation.

Present Illness.—April 18, 1946, the patient complained of anorexia, fever, and running nose. Nosebleeds were of unexplained origin. The patient was well up to this time. She had infrequent abdominal pains. The skin was always sallow. The spleen was palpable to within three fingerbreadths below the costal margin in the nipple line. The patient was slightly undernourished but otherwise normal.

Listed below are dates of transfusions and data obtained from laboratory reports, etc.:

On April 19, 1946, hemoglobin was 8.1 Gm. (48 per cent), red blood cells 2,450,000, white blood cells 6,700, polymorphonuclears 46 per cent, lymphocytes 48 per cent, monocytes 5 per cent, eosinophiles 1 per cent. There was considerable anisocytosis and eccentric achromia, many microcytes, few poikilocytes, many cells showing marked polychromatophilia, no basophilic stippling or nucleated red blood cells with marked degree of anemia, microcytic hypochromic type, with tendency to leucopenia. Blood picture was of congenital hemolytic icterus. Fragility at beginning hemolysis was 0.48 per cent and at complete hemolysis was 9.42 per cent. The icterus index was 75. Van den Bergh direct reaction was negative, the indirect was 2.0 mg. per 100 c.c. On April 21, 23, 25, 29, and 30, 250 c.c. citrated blood were given. On April 21 hemoglobin was 40 per cent, red blood cells 2,290,000, white blood cells 6,600, polymorphonuclears 44 per cent, lymphocytes 50 per cent, monocytes 4 per cent, eosinophiles 1 per cent, basophiles 1 per cent. On April 23, hemoglobin was 51 per cent, red blood cells 2,870,000, white blood cells 6,500, polymorphonuclears 58 per cent, lymphocytes 39 per cent, monocytes 2 per cent, eosinophiles 1 per cent. On April 25, hemoglobin was 65 per cent, red blood cells 3,670,000, white blood cells 7,200, polymorphonuclears 59 per cent, lymphocytes 38 per cent, monocytes 2 per cent, eosinophiles 1 per cent. Operation was on April 29. On April 30,

hemoglobin was 72 per cent, red blood cells 3,710,000, white blood cells 27,500. polymorphonuclears 89 per cent, lymphocytes 10 per cent, monocytes 1 per cent. On May 4, hemoglobin was 75 per cent, red blood cells 3,910,000, white blood cells 10,400, polymorphonuclears 80 per cent, lymphocytes 18 per cent, monocytes 1 per cent, basophiles 1 per cent, occasional microcytes, poikilocytes. The icterus index was 24. The Van den Bergh direct reaction was immediate positive, the indirect was 3.1 mg. per 100 c.c. On May 6, the icterus index was 10 and the Van den Bergh direct reaction was negative, indirect, 1.1 mg. per 100 c.c.

Synopsis of Operative Procedure, April 29, 1946.—A transverse incision was made in the upper left quadrant through which the abdomen was explored. The findings were essentially negative except for a markedly enlarged spleen which was easily mobilized. The spleen was about three times normal size. Some fine peritoneal adhesions were separated. The pedicle was exposed, the vessels clamped, divided and ligated separately with #1 chromic double suture following which a sponge was placed in oozing area until the appendix was removed.

Pathologist's Report by Dr. Oscar B. Hunter.—Grossly, the spleen is considerably enlarged, measuring 12 cm. in length by 9 cm. in width by 6 cm. in thickness and weighing 217 grams. The capsule is slate gray in color after fixation and is definitely thickened. Sections through the spleen reveal a firm splenic pulp. It is quite meaty in consistency and numerous enlarged follicles are noted. No gross evidence of infarction or involvement other than splenomegaly is noted.

Sections from the spleen reveal some thickening of the capsule, and characteristic fibrous tissue trabeculae extending into the splenic pulp. Some areas show increased fibrosis throughout the sections studied and in most parts of the spleen the pulp is completely filled with red cells. The splenic corpuscles are fairly characteristic in some instances, showing a typical follicular arrangement of the lymphoid cells, while in others the lymphocytes are more or less scattered. The sinuses in most instances are thickened and some contain small amounts of blood. The picture is that of a spleen in a case of congenital hemolytic icterus.

These two patients recovered rapidly and mark but one generation of the disease in the family. There was no evidence of paternal stigma. By pursuing the family history we have assembled the following data which we present as evidence that four known generations of this family have suffered from the disease.

1. The mother of our second patient, J. G., was operated on at the George Washington Hospital by Dr. Stewart M. Grayson in 1943, when a diagnosis of acholuric jaundice was made and a splenectomy performed. This is a second generation.

2. In a communication from this family's physician, Dr. Sarah Peyton, verification was received that Mrs. C., the mother of Mrs. J. G., and the maternal grandmother of B. S. and S. G., has the disease, with the concomitant findings of cholecystitis with cholelithiasis, the usual complication of the disease in older people. This is the third generation.

3. Although complete data cannot be assembled for the fourth generation, we have the history from communications from Mrs. C and the family physician, Dr. Sarah Peyton, in which they state that the maternal great-grandmother had fever and jaundice of marked degree at times. The jaundice and fever varied in intensity as she underwent a series of crises in the disease. She was known to have had the disease from early childhood and at death the undertaker noted that, "she had the smallest amount of blood I have ever seen."

Two main indications for early splenectomy as the primary treatment for this disease are: (1) the high incidence of cholelithiasis; and (2) the prevention of hemolysis and blood destruction, as marked improvement has been observed in those upon whom splenectomy was performed. Barber,³ in a series of cases in one family, confirmed the finding that the anemia and jaundice disappeared rapidly, though the fragility of the red blood cells continued for an indefinite time following the splenectomy.

CONCLUSIONS

1. Confirming previous observations, definite evidence of the part heredity plays in this disease has been shown by its appearance in two first cousins (splenectomy), their aunt (splenectomy), their grandmother (icterus-anemia) and their great-grandmother (icterus-anemia), all maternal, representing four generations of the same family.

2. Blood studies on all members of a family are indicated when the diagnosis has been made in any one.

3. Preoperative transfusions give no sustained improvement and are palliative.

4. Early splenectomy, followed by transfusions, promotes convalescence and sustained improvement.

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AN UNUSUAL ERUPTIVE FEVER INVOLVING THE SKIN AND MUCOUS MEMBRANES

ITS RELATION TO AND THE STATUS OF THE SO-CALLED STEVENS-JOHNSON DISEASE
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IT IS our purpose to present a case of an unusual systemic infection with an eruptive fever involving the skin, eyes, lips, buccal cavity, and urethral meatus. In addition, we shall discuss its relation to a small group of similar, previously reported cases, with particular reference to those in the category of the so-called Stevens-Johnson disease.

Full credit has been given to von Hebra¹ (1866) for describing the erythema multiforme exudativum group, although Bazin² (according to Keil³) was the first to recognize the occurrence of lesions in the mouth and the prodromal constitutional symptoms in the vesiculobullous type of erythema multiforme exudativum. Undoubtedly von Hebra¹ also underestimated the attendant severity of a small number of these cases. Early reports with involvement of the eye include those of Fuchs,⁴ Hanke,⁵ and Bergmeister.⁶ Hanke's case terminated fatally. Then, in 1922, Stevens and Johnson⁷ cited two cases of a "new eruptive fever associated with stomatitis and ophthalmia;" the skin eruption here is described as "extraordinary" and "unlike any hitherto described." With the appearance of this paper, new interest was aroused in the erythema multiforme group, especially in America. For this Stevens and Johnson are to be given full credit, although they were mistaken as to the "newness" of their report. Following this, a wide variety of cases (but a small number) has been noted in the literature as Stevens-Johnson disease. Almost at once a controversy arose and still exists concerning the usefulness of and necessity for the new term. There are those who prefer to regard Stevens-Johnson disease as a type of erythema multiforme exudativum (Hebra) rather than as a distinct entity. The authors hold the first opinion for reasons which will be discussed later in this paper. In this belief, we are in agreement with Fletcher and Harris,⁸ Weisberg and Rosen,⁹ Keil³ and others. Givner and Ageloff,^{10, 11} Murphy,¹² Patz,¹³ and Nellen,¹⁴ among others, hold the opposing view. The following case report will be of interest to all, however, because of its comparative rarity.

E. W. L., an 8-year-old boy of Jewish parentage, was admitted to the hospital on Dec. 19, 1946, with the chief complaint of a sore mouth. Five days before admission, the patient suddenly complained of malaise, nausea, sore throat, and pain in the stomach. The oral temperature was 102° F. The throat and buccal mucous membranes appeared inflamed. A physician prescribed a mixture of aspirin, phenacetin, and caffeine. The next day a mild, infrequent, nonproductive cough appeared, together with severe anorexia and

pain on swallowing. In the succeeding forty-eight hours, all the symptoms persisted, with only slight improvement in the patient's condition. During this period the patient vomited several times, the contents being either mucus or food. The temperature remained elevated between 100° and 101° F. A mucoid nasal discharge, which had been present at intervals for the previous two months, increased in severity. On the day prior to admission, the temperature quickly climbed to 104.6° F.; the boy became somewhat toxic and an increased respiratory rate was noted. Oral penicillin (50,000 units) every two hours and nose drops were begun. That evening the patient was first seen by one of us (R. A. S.) in consultation. No significant new findings were observed except for swollen lips and small hemorrhagic areas on the hard palate and buccal mucous membranes. The patient was given 6 c.c. of gamma globulin intramuscularly, because of the possibility of invasion by hemorrhagic measles. Examination of the blood by a private laboratory showed a hemoglobin of 70 per cent, a red-cell count of 5,940,000 and a white-cell count of 11,150 with 13 per cent adult neutrophils, 46 per cent young forms, 40 per cent lymphocytes, and 1 per cent monocytes. The platelet count was 248,000. The patient was admitted to the hospital on the following day with the diagnosis of an acute virus infection, etiology to be determined.

The past history revealed a fever of undetermined origin at the age of 3 years, with chicken pox two years later. The boy had been immunized against diphtheria, smallpox, tetanus, pertussis, and typhoid fever. Two months prior to the present episode, the patient recovered from infectious mononucleosis. There was no known recent exposure to measles, although a neighboring child had mumps "several weeks" past. However, there was a history of contact two weeks prior to this illness with three dogs, two of which were ill with fever and cough; and were subsequently diagnosed by a veterinarian as a "streptococcus sore throat," although no cultures were taken. The family history was noncontributory.

Physical examination revealed a patient who appeared acutely ill, complaining bitterly of a sore mouth and photophobia. There was a moderately severe conjunctivitis, but no ocular discharge. The nasal mucosa were distinctly swollen and congested; a mucoid nasal discharge was present. The lips were dry and swollen. On the buccal mucous membranes, including the hard and soft palate, were many small, whitish areas of necrotic mucous membrane. The pharynx was injected; a small amount of mucopurulent exudate was seen in the throat. The tongue was dry and coated white. The anterior and posterior cervical lymph nodes were enlarged; the axillary and inguinal nodes were small and shotty. Examination of the chest revealed many medium and coarse dry inspiratory râles over the right posterior hemithorax from the fourth dorsal vertebra downward; the percussion note in this area was hyporesonant, with increased breath sounds. The spleen was not palpable. There was no hepatomegaly. On the skin of the volar and dorsal surface of the right hand were seven erythematous papules; on the left knee were several minute vesicles surrounded by a rim of erythema. The rectal temperature was 104.8° F., the pulse 140, and the respirations 38 per minute.

Examination of the blood showed hemoglobin of 11.5 Gm., red-cell count of 4,620,000 and a white-cell count of 13,000 with 85 per cent neutrophiles (of which half were young forms) 10 per cent lymphocytes and 5 per cent monocytes. A routine urinalysis disclosed a faint trace of albumin, with a few white cells and bacteria in the sediment. A Rumpel-Leede test was negative. Blood cultures were sterile. A nasopharyngeal smear showed gram-positive cocci and diplococci; the culture revealed hemolytic streptococci, pneumococci, and *Staphylococcus albus*. A conjunctival smear and culture were negative. A portable chest x-ray film was negative.

Penicillin by intramuscular route in the dose of 25,000 units every three hours was begun at once owing to the possibility of a secondary infection as evidenced, for example, by the marked increase in neutrophiles. In addition, general supportive care was ordered, including frequent use of mouthwashes, intravenous fluids, and blood transfusions.

On the second day the patient seemed worse. The temperature, after an early morning drop to 100.5° F. (rectally), rose to a maximum of 106.2° F. (rectally). At this time the boy was alternately drowsy and very irritable. Examination revealed an increase in the extent of the skin lesions. Present on the posterior aspect of both upper thighs, anterior surface of the left thigh, dorsal surface of the left arm and right elbow were numerous small (1 to 2 mm.) vesicles, containing a clear fluid, surrounded by a rim of erythema varying in size from 0.2 mm. to over 1 cm. The skin about the urethral meatus was inflamed, but no discharge was evident. Both lips, particularly the lower, showed extensive, raw, bleeding areas with crust formation. There was no significant change in the oral lesions. A right subconjunctival hemorrhage was present; the conjunctivitis was more severe. The patient refused to take any food or fluids by mouth because of the marked soreness of the mouth and throat. His cough increased in severity and frequency. Fortunately, the temperature dropped to 99° F. by evening. In view of the character of the lesions, a diagnosis of herpes stomatitis was suggested, with spread of the herpes virus throughout the body, probably through the blood stream. Accordingly, specimens of saliva were sent to the Virus Diagnostic Research Laboratory of the Children's Hospital, Philadelphia, where tests were performed on rabbit corneas and in chick embryos. These, however, yielded no evidence of the herpes virus. Blood sent for virus neutralization tests eventually proved also to be negative. It was impossible to obtain fluid from the vesicles because of their minute size.

During the first four days, feedings were almost entirely by the parenteral route. Slowly the patient accepted increasingly larger amounts of nourishment orally so that all intravenous fluids were discontinued on the eighth day. Local eye therapy included frequent boric acid compresses and the instillation of one drop of colloidal silver solution (10 per cent) three times daily. With this, the conjunctivitis steadily improved, finally disappeared by the tenth day. After the second day, the rectal temperature rose to 103° F. on only one occasion (third day) and then slowly subsided by lysis, remaining less than 100° F. (rectally) from the fifteenth day until discharge.

On the third day, the skin lesions began to dry, the lips appeared swollen but dry with some areas of sealing and other spots where the surface epithelium was eroded. The whitish necrotic areas in the mouth gradually sloughed, leaving raw areas which bled easily. By the eighth day brown scabs surrounded by an area of erythema had formed at the site of all the formerly vesicular lesions. The oral lesions had almost entirely cleared, except for an ulcer on the frenum of the tongue. The lips were much less swollen, with a few small areas of superficial epithelial erosion present. The cough was gone. Penicillin was discontinued on the tenth day, a total of 1,625,000 units having been given. Later (eleventh day), the scabs fell, leaving pinkish-brown spots which gradually faded. A white cell count on the thirteenth day was 10,500 with 67 per cent neutrophils (of which 91 per cent were filamented) 29 per cent lymphocytes and 4 per cent monocytes. The patient was discharged on the eighteenth day apparently in perfect health.

It is of interest here to note that, although we were unable to implicate the herpes virus as the causative agent in this patient's illness, we are not the first to suggest an etiologic relationship between herpes simplex and erythema multiforme. In America, Anderson¹⁵ (and before him Forman and Whitwell¹⁶ in England) had suggested such an association.

The history of contact with sick dogs has not been reported previously, to our knowledge, in this group. Careful questioning in future cases may bring to light the importance of animal contact. It is well known, moreover, that children are likely to have much closer association with animals than have adults. This may be the cause of the greater incidence of severe forms of erythema multiforme exudativum (Hebra) in children.

The early use of penicillin in adequate dosage may have been of value in preventing the complications of secondary infection. We do not believe it had any direct effect on the illness. Goldfarb¹⁷ noted that decided improvement in his case seemed to be related in time to the use of penicillin, especially locally.

DISCUSSION

In our attempt to diagnose this case, our attention was soon centered on the erythema multiforme exudativum (Hebra) group and then to the consideration of the so-called Stevens-Johnson disease. According to Keil,³ the cutaneous lesions of erythema multiforme exudativum (Hebra) can be conveniently classified, for clinical purposes, into the maculopapular and the vesiculobullous types, although, it must be cautioned, both variants may occur in the same patient simultaneously, in subsequent crops, or in later recurrences. In an excellent paper Fletcher and Harris⁸ set down the criteria for the diagnosis of erythema multiforme exudativum (Hebra)—bullous type as follows:

1. Multiform erythematous skin lesions.
2. Bullous formation on the skin or mucous membranes.
3. Constitutional symptoms compatible with an acute infectious disease.

If we substitute the word "vesicle" for "bullous," the relation to this case is manifest. Fletcher and Harris⁸ classify individual cases, moreover, into mild, moderately severe, severe, and grave forms.

Only on search of the literature of Stevens-Johnson disease did we realize with how vague an entity we were dealing. The differences in the material described are quite extreme and the criteria laid down by the various authors for its diagnosis are so conflicting that it makes one wonder whether Stevens-Johnson disease is a distinct entity. This confusion has arisen, we believe, partly from indiscriminate efforts to extend the scope of the disease as defined by Stevens and Johnson themselves; and partly from the belief that the term Stevens-Johnson disease is synonymous with erythema multiforme exudativum (Hebra)—vesiculobullous type, or by some, with the entire erythema multiforme group. There is no question that Stevens and Johnson described a serious form of erythema multiforme, a form which only infrequently occurs and which had not been well recognized before their paper. This is not sufficient reason, however, to call it a distinct entity.

It is our hypothesis with regard to much of the erythema multiforme group that we are dealing with an infection by organisms of a similar type, probably viral in nature, and with a hematogenous spread. One must consider here in parallel the known example of measles which exhibits definite, though at times atypical, cutaneous lesions. The multiform cutaneous lesions of the group under discussion may be, in truth, merely manifestations of the same systemic infection differing only because of other factors involved, such as the virulence of the invader, the degree of resistance of the host, and others, presently known and unknown. Morphologic classifications of disease will be, we trust, only temporary standards. Thus, in the inorganic class of noxious agents, it is well known that the cutaneous lesions of chronic arsenic poisoning may be of almost any type.

As a baseline for further discussion, we shall summarize the two cases presented by Stevens and Johnson and attempt to point out the particular emphasis they placed on certain aspects of their cases. Both cases occurred in young boys, both had a high and prolonged fever, and both a purulent conjunctivitis. (This last is considered important not only by Stevens and Johnson, but also by later investigators). It is the skin eruption, however, which highlights the report, being described as "extraordinary" and "unlike any hitherto described." The rash appeared first on the back of the neck and chest, spreading to the face and extremities but not to the scalp during a period of eighteen days. The lesions were first dark red oval macules varying from 0.5 cm. to 2 cm. in their longest diameter and without areolae. In a few days these macules became brownish purple papules, some of which acquired yellow, dry, necrotic centers. Vesicles and pustules were absent. Later, the lesions changed to dark brown, horny, thick scales with raised, papery edges. (This change was considered by the authors to be of diagnostic significance). From the fourth week, the scales dropped off, leaving faint pigmented areas without pitting or scarring. We contrast this with the exanthem and absence of a purulent conjunctivitis in our case.

Concerning the oral lesions, it is recorded in Case 1 that the oral mucous membranes were inflamed and showed small bullous lesions which rapidly broke down, leaving a raw and angry surface. No mention is made of this

aspect again in the entire case report. In Case 2 it is recorded that when the patient was at another hospital the mucous membrane of the mouth was practically exfoliated. On the twenty-third day, when Stevens and Johnson apparently first saw the patient, no statement is made concerning any oral lesions. From this we conclude that Stevens and Johnson emphasized only the presence of a stomatitis, not of a particular type, as bullous or membranous. Moreover, in the summary of their paper, we find no statement of bullous lesions, whether on the skin or mucous membranes. We mention this point particularly because of the impression obtained on reading later papers (as Kove,¹⁸ Murphy,¹² and Nellen¹⁴), that the presence of a bullous or vesicular lesion is a cardinal factor in the diagnosis of Stevens-Johnson disease. Our viewpoint is substantiated by the fact that in Wheeler's¹⁰ case, which was seen by Stevens himself, no bullae were noted. Again, it is the exanthem and not the oral lesions which seem to have been the striking element. Wheeler¹⁰ states, "Scattered over the body were brownish spots unlike anything I had seen."

We agree with Keil³ that the symptoms described would place the so-called Stevens-Johnson disease within the category of the maculopapular type of erythema multiforme exudativum (Hebra). Ginandes,²⁰ in an early paper declares, "I am not certain that the differences are sufficiently striking to warrant such a separation [i.e. to regard Stevens-Johnson disease as a separate entity—*author's note*]. One finds, rather, sufficient resemblance in all these cases to believe they more probably belong to the same group."

With regard to the degree of ocular involvement, there are already several conflicting opinions. Duke-Elder²¹ regards Stevens-Johnson disease as a form of ocular erythema multiforme with a purulent conjunctivitis. Jones, Talbot, and King²² are in agreement and express the opinion that Stevens-Johnson disease should be reserved for those patients presenting a purulent conjunctivitis, stomatitis, and a cutaneous rash without the formation of an (ocular) membrane. This would apparently exclude such cases as those of Ginandes,²⁰ Patz,¹³ Givner and Ageloff,¹¹ (Case 1), Rutherford,²³ and Kove¹⁸ (Case 2). In addition, what are we to do with the reports of Grossman²⁴ (Cases 1, 4, and 5), and Umiker and Crofoot,²⁵ where only a catarrhal conjunctivitis was present? Or those of Levy²⁶ and Grossman²⁴ (Case 6) with no ocular involvement? Are these "true" Stevens-Johnson disease? In contrast to Duke-Elder,²¹ Erger²⁷ states, "Numerous degrees of eye involvement have been reported, ranging from simple catarrhal conjunctivitis to ocular destruction."

We find no unanimity of opinion in regard to the cutaneous lesions, either, in spite of the emphasis placed by Stevens and Johnson on this point. Descriptions have ranged from no exanthem at all (Kove,¹⁸ Case 1 and Wentz and Seiple,²⁸ Case 1) to unusual combinations of macules, papules, vesicles, petechiae, and bullae. Erger²⁷ remarks, in contrast, that the cutaneous lesions are more likely to be uniform than multiform. Grossman²⁴ described four cases, in which the cutaneous manifestations, vesicular and bullous in nature, were confined to the penis and lips.

It would appear, then, that the effort to have the small, round peg of "Stevens-Johnson" disease fill the large, square hole of erythema multiforme

exudativum (Hebra) has resulted only in confusion. If the term Stevens-Johnson disease is to be used at all, whether one considers it a distinct entity or only a variant of erythema multiforme, the diagnosis should be strictly reserved for these cases, otherwise unclassifiable, presenting: (1) constitutional symptoms resembling an acute infectious disease; (2) multiform erythematous skin lesions, predominantly of a maculopapular nature; (3) a purulent conjunctivitis without the formation of an ocular membrane; (4) a stomatitis.

The differential diagnosis rests mainly among hemorrhagic measles, small-pox, syphilis, dermatitis herpetiformis, pemphigus, agranulocytosis, septicemia, and Vincent's angina.

SUMMARY

A case of an unusual eruptive fever associated with conjunctivitis, stomatitis, nasopharyngitis, and urethral meatitis is presented. A history of contact with sick dogs is reported, apparently for the first time, in this group of cases. Studies to incriminate the herpes virus as the etiologic agent were negative. The status of the so-called Stevens-Johnson disease is reviewed and defined more clearly. The conclusion is reached that Stevens-Johnson disease is only a form of erythema multiforme exudativum (Hebra) and not a distinct entity. The hypothesis is put forward that, with regard to much of the erythema multiforme group, that we are dealing with an infection by organisms of a similar type, probably viral in nature. The multiform cutaneous lesions may be, in truth, merely manifestations of the same systemic infection.

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CONGENITAL HYPERTROPHIC STENOSIS OF THE DUODENUM

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A CONDITION best listed under the nomenclature of congenital hypertrophic stenosis of the duodenum has been encountered in two infants, one of whom was seen twelve years ago, and the other recently. A fairly thorough search of the literature, with the assistance of the staff of the Library of Los Angeles County Medical Association, has failed to reveal any previous report of the condition. Several forms of duodenal obstruction at birth or in early infancy have been discussed, but none of this particular variety, in which the findings are so strikingly similar to those ordinarily encountered at the pylorus, has been mentioned.

Each of the patients discussed in this paper had a fusiform swelling about $1\frac{1}{4}$ inch in length, whitish, smooth, composed of abnormally hypertrophied muscle, and of a consistency halfway between gelatine and cartilage, the duodenal wall being thickened to a depth of $\frac{3}{16}$ inch or so, the lumen being constricted until the edematous mucosa was bunched up into a practically impassable mass. All of this is characteristic of the fairly common stenosis of the pylorus, but in these cases it was confined to the first portion of the duodenum, with no encroachment on the pylorus.

Both of these patients were male infants. Both were treated by longitudinal myotomy (Rammstedt) down to mucosa: in both cases the mucosa was inadvertently opened and repaired by suture; and in both cases the babies survived and had no more obstructive symptoms.

The chief anatomic difference between the two infants was that the first one had a constriction at the midportion of the tumor, as if a band had at one time almost completely encircled it, this constriction being practically the full depth of the tumorous bowel wall. It was at this thin place that the mucosa was entered during surgery.

The first infant was seen in 1935, at about 4 weeks of age. Normal at birth, he began vomiting at 10 days of age, but, despite increasing emesis, weighed the same as he had at birth at 3 weeks of age, and continued to gain to 1 pound, 6 ounces over birth weight when operated upon at 6 weeks of age. Observation was not alert enough at this time to note whether there was any bile in the vomitus or not. Operation was done because thick cereal feeding and atropine had been unavailing in stopping the projectile vomiting, and because there were large visible peristaltic waves.

The second patient, seen in 1947, arrived at surgery at 4 weeks of age, after a very confusing course. A firstborn infant, delivered at term by a very difficult breech extraction, he was in severe shock and depression at birth, with right facial palsy, partial third nerve paralysis, and presumptive cerebral edema.

He rallied well, however, and although the paralysis persisted, arousing suspicion of spasticity, and an occipital cephalhematoma and hemorrhage into the sheath of the right sternomastoid muscle developed, he took his bottle well and had gained back to birth weight at 2 weeks of age, when vomiting began. Concentrated feedings were tried without improvement. Phenobarbital was used, but .

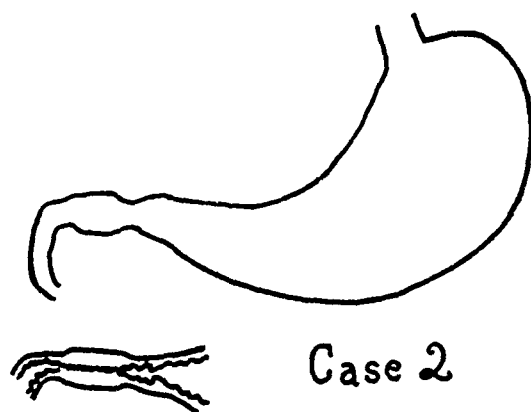
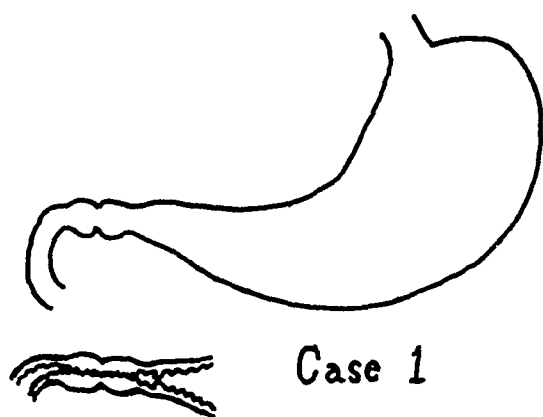


Fig. 1.

its only effect was to throw him into profound stupor bordering on coma, which lasted for several days after it was discontinued. The vomiting became rapidly worse until it was practically total when the infant reached 3 weeks of age. Vomited material seemed to be stained yellowish at times. There was never any distention. There were no peristaltic waves visible at any time, nor was a tumor felt, although it was noted verbally at one time that up under the liver edge something harder than normal and rather pecan-shaped seemed to meet the examining fingertips. X-ray of the abdomen in a vertical position showed

no pools of fluid in intestinal loops and very little gas below the stomach. A little normal stool came through on suppository or enema for several days. Because of lack of evidence of obstruction, neurosurgical consultation was obtained. Subdural hematoma was ruled out and it was the opinion of the neurosurgeon that little if any severe brain damage had been done, and that this would probably clear up in time. Meanwhile, the baby was being sustained on intravenous amigen and glucose, and remained in surprisingly good hydration and general condition. The issue was determined as calling for surgical exploration when the baby, at 4 weeks of age, began to pass dark stools which quickly became tarry mucus only.

Case Reports

OMPHALOCELE

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A SMALL umbilical hernia is a condition that is frequently encountered in infancy. Large hernias of the umbilical cord containing several loops of intestine with or without other abdominal organs are quite rare, however. Such large hernias, called omphaloceles, or umbilical eventrations, occur approximately once in every 5,000 to 10,000 births. As would be expected, unless the eventration is surgically repaired soon after birth, the mortality rate is almost 100 per cent. In the largest series of infants treated surgically,¹ the mortality rate was 49 per cent.

Jarcho² extensively reviewed the literature on omphalocele up to 1937 and described a patient (in whom the hernial sac contained liver) who was successfully treated by surgery. In 1940, Gross and Blodgett¹ reported twenty-two patients with the condition, ten of whom were still alive at the time of publication of their report. None of their patients lived, however, when the hernial sac had ruptured and peritonitis had occurred. A search of the literature likewise revealed no reported survivals following rupture of the sac. The following report on a patient with umbilical eventration who lived following surgery is presented because of the severe complications that occurred and the method of treatment that was used.

CASE REPORT

Baby A, the second child of a 21-year-old white woman, was delivered by low forceps at term after a labor of eight hours. The baby weighed 6½ pounds and had a defect 4.5 cm. in diameter in the abdominal wall in the region of the umbilicus, through which about two feet of the small bowel, cecum, and part of the stomach had passed (Fig. 1). No skin or covering was present over this defect. During the process of delivery the peritoneal covering of the hernial sac had apparently ruptured and the intestines had become exposed so that they were contaminated by the mother's perineum. Immediately following completion of the delivery, the baby was put in a sterile sheet and the intestines were covered with sterile packs soaked in physiologic saline solution. Approximately two hours later the intestines were replaced into the abdominal cavity and the defect was closed surgically in three layers. No immediate respiratory distress was noticed following the replacement of the intestines into the abdominal cavity and the baby was returned to the ward in good condition.

The patient was kept in an incubator for the first few days and was given oxygen continuously as well as 30,000 units of penicillin intramuscularly every three hours, since the intestines were known to have been contaminated during the delivery. Beginning at twelve hours of age, water was offered by bottle every three hours. The child nursed well, but several minutes after being fed it regurgitated bile-stained material and abdominal distention began to occur. In view of the apparent partial intestinal obstruction, the minimum daily fluid requirements were thereafter administered parenterally. Because regurgitation

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Fig. 1.—Picture of patient at birth showing 4.5 cm. umbilical defect with stomach, small bowel, and cecum protruding.



Fig. 2.—X-ray of patient taken on third day of life showing marked distention of stomach and several loops of bowel in left lower quadrant.

of bile-stained material following oral feedings persisted, x-rays were taken on the third day of life. These revealed marked distention of the stomach and several large loops of bowel in the left lower quadrant (Fig. 2). Barium given orally remained in the stomach after six hours, although some seemed to appear in the small bowel. Wangensteen gastric suction was instituted in view of the x-ray findings and parenteral fluid therapy was continued. Intravenous plasma was given approximately every other day in addition to subcutaneous solutions.

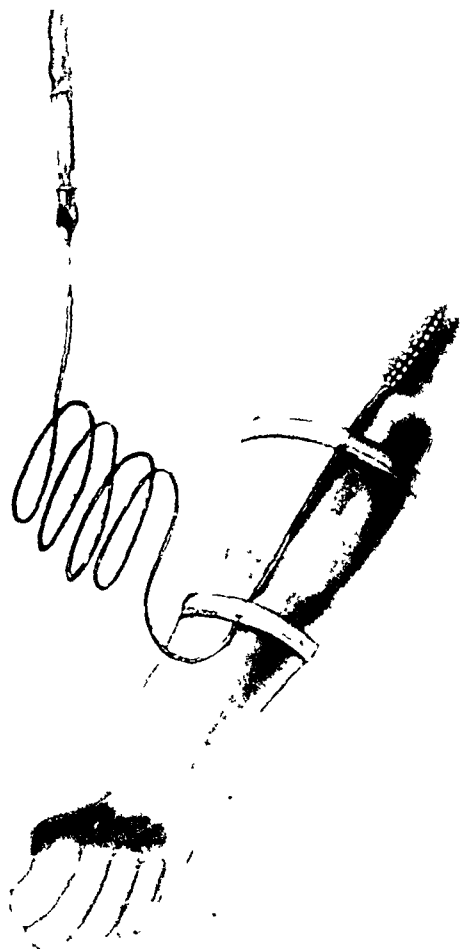


Fig. 3.—Drawing illustrating use of ureteral catheter for constant intravenous transfusion. After cut-down on vein, catheter is inserted several centimeters, as shown by dotted lines, other end of catheter is connected to intravenous tubing by No. 23 needle. Note length of catheter permitting free movement of extremity.

In spite of continuous gastric suction and parenteral fluids, the baby's abdomen remained distended. On the sixth day of life barium was again given by mouth and followed under the fluoroscope in an attempt to find an area of obstruction. The barium remained in the stomach for the most part, but some was seen to pass through the duodenum, jejunum, and into the left lower quadrant of the pelvis, beyond which no barium would pass.

In view of the definite evidence of obstruction by x-ray, and since the baby already had one known congenital defect, it was thought that further defects such as intestinal atresia or stenosis might be present. Accordingly, on the ninth day of life the baby's abdomen was explored surgically under ether anesthesia. Upon opening the peritoneum a generalized peritonitis was encountered. Loops of small bowel were adhered together and several large



Fig. 4.—Picture of patient one month following discharge from hospital. Defect is well healed.

abscesses were present in the roots of the mesentery: one abscess was causing intestinal obstruction in the left lower quadrant. The abscesses were incised and drained and the abdomen was closed with difficulty using #36 steel wire and chromic catgut. The baby was returned to the ward in semishock.

For the next seven days following the abdominal exploration and drainage of the abscesses, the baby's condition was critical. It was obvious that the baby would have to be fed parenterally over a long period of time and so a cut-down was made on the right cubital vein and a #4 ureteral catheter was inserted 21½ inches up into the vein. The catheter was inserted this distance so as to offset any possibility of its coming out during the several

days that it was to remain in place. The catheter was taped securely to the arm and the baby was allowed to move the extremity at will (Fig. 3). During the next seven days the baby received plasma or whole blood through the catheter continuously, in addition to calculated amounts of 5 per cent glucose in saline or distilled water, vitamin B complex, ascorbic acid, vitamin K, and penicillin. Gastric suction was maintained for five postoperative days, after which time small amounts of glucose water were offered by bottle every two hours. Gradually the oral amount was increased as well as the time interval between feeding so that by eight days postoperatively the baby was taking 3 oz. of formula every three hours without regurgitation. Parenteral feedings were subsequently discontinued.

Postoperatively the abdominal incision broke down and became infected. This was treated satisfactorily at first with magnesium sulfate soaks and later with penicillin soaks. The baby was discharged from the hospital at 35 days of age in only fair nutritional condition, but he was eating well. On a standard formula, multiple vitamins, iron, and good care by the parents the baby improved remarkably in one month (Fig. 4). When last seen at 7 months of age the baby weighed 16½ pounds and was developing normally. Only a questionable defect was present in the anterior abdominal wall.

SUMMARY

1. Omphalocele of the umbilical cord occurs rarely and has a high mortality rate unless repaired early.
2. A successfully treated case of omphalocele which did not have a peritoneal covering is reported.
3. The case is remarkable because of the complicating mesenteric abscesses and peritonitis.
4. A method of continuous administration of intravenous fluids through a ureteral catheter is described.

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HEMANGIOMA OF THE LIVER CAUSING DEATH IN A NEWBORN INFANT

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RUPTURE of a hemangioma of the liver is seldom considered in the differential diagnosis of shock in the newborn. Indeed, the condition is rare. Shumacker,¹ in a review of hemangioma of the liver, presented only two cases affecting newborn infants: one occurred in a 7-day-old infant reported by Hammer,² and the second in a 3-day-old newborn infant reported by Kissinger.³ No other cases have been reported in recent literature.

Cavernous hemangioma of the liver is described as the most common benign tumor of the liver, yet there are rarely any ill effects, it usually being an incidental finding at autopsy.⁴ Moreover, it is more common in adults where it may occasionally produce hepatic enlargement. Montgomery⁵ states that trauma to the abdomen may cause a rupture of the tumor and a serious hemorrhage. This may have been a factor in the following case.

CASE REPORT

H., a boy, was born at 11:05 P.M. on June 21, 1947. The mother had no antepartum abnormalities; her Kahn test was negative and the Rh factor positive. The labor was extremely long and was complicated by a transverse position of the presenting head with a midpelvic arrest. At birth the infant's respirations and cry were spontaneous and immediate and the general condition was good. He was a full-term baby, weighing 7 lb., 4 oz.

An examination at thirty-six hours after birth showed a newborn child who was apparently normal: the color was pink, the cry lusty, respirations normal, Moro reflex active, tonus good, and there were no anomalies.

The baby's condition was considered to be good until the nurse noted him to be unduly pale at 2 A.M. on June 24, when 51 hours of age. Respirations were slow but were of good depth and the baby cried loudly when spanked. A heat cradle was applied. A few minutes later the cry was weaker and he was placed in an incubator and oxygen given. By 3 A.M. the condition was critical. The skin and the mucous membranes were extremely pale. Respirations were gasping in nature, and there were long periods of apnea. The heart sounds were inaudible. Tonus was poor. The abdomen was flat and the wall slightly tense. The anterior fontanel was not bulging. The impression was that he had experienced a sudden massive internal hemorrhage with resulting anemia and shock. Because of the extremely long and difficult labor, a massive intracranial hemorrhage seemed likely. Vitamin K, one milligram, was given intramuscularly. An emergency blood typing and cross-matching and a complete blood count were requested. When the blood had been prepared, the condition was so grave that it seemed certain that death would result immediately if a venesection were done. The baby died at 6:33 A.M., four and one-half hours after the appearance of the first signs of illness and after 55½ hours of life.

The laboratory reports were: erythrocytes, 3,410,000; hemoglobin, 9.9 Gm. or 68 per cent; leucocytes, 11,750, 44 per cent being polymorphonuclear. No abnormal cells were found.

The post-mortem examination showed a well-developed and -nourished newborn infant with pale skin and slightly distended abdomen. The pleural and

pericardial cavities were negative. Scattered petechial hemorrhages were found beneath the visceral pleura.

On opening the peritoneal cavity there was found an estimated 350 c.c. of old dark blood, some of which was clotted. The peritoneal surfaces were normal. The liver presented the most significant findings. It was determined to be the site of the hemorrhage and the source of the blood in the peritoneal cavity. On the inferior surface of the liver, posterior to the gall bladder, was a large clot of blood measuring 8 cm. in its greatest diameter. The edge of the clot was continuous with the substance of the liver, indicating that the clot was beneath the capsule. The liver was a pasty yellow color on cut section. The gall bladder was normal.

There were no other significant gross findings except 15 to 20 c.c. of old blood, which was found beneath the tentorium cerebelli.

Microscopic examination.—There was a rather large amount of hemorrhage throughout all sections of the lungs, and no evidence of an infectious process. Serial sections through the liver revealed a rather remarkable finding. There were a large number of blood islands which could be seen throughout the liver substance along with evidence of parenchymatous and fatty degeneration. At one portion at which the previously described clot was adhered to the liver was a large hemangioma with hemorrhage, necrosis, and thrombosis within the hemorrhagic areas adhered to the liver substance.

The anatomic diagnosis was: (1) hemorrhagic disease of the newborn, and (2) hemangioma of the liver with hemorrhage, necrosis, and thrombosis.

The cause of death was severe peritoneal hemorrhage due to rupture of a hemangioma of the liver.

CONCLUSIONS

A fatal case of rupture of a hemangioma of the liver in a 2-day-old infant is reported.

The rupture may have been initiated by trauma incident to a difficult labor and complicated by hemorrhagic disease of the newborn infant.

Rupture of a hemangioma of the liver is to be considered in the differential diagnosis in cases of internal hemorrhage in the newborn infant.

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CONGENITAL TUBERCULOSIS

A REVIEW OF THE DISEASE WITH REPORT OF A CASE

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IT IS a generally accepted medical fact that, with the exception of syphilis, prenatal infection by placental transmission is relatively rare. There are, however, cases on record of prenatal or natal smallpox, chickenpox, measles, tuberculosis, typhoid fever, and pyogenic infections.

In 1938, Conrad¹ gave this definition of congenital tuberculosis: "Tuberculosis in which the infection occurs before birth by way of the blood stream, or at birth by the aspiration of tuberculous amniotic fluid or tuberculous matter present in the birth canal."

It would seem that for the infection to be truly congenital, all cases occurring from aspiration of infected material at the time of birth should be excluded, because this type of infection would more properly be classified as acquired tuberculosis. However, true congenital tuberculous infection of the fetus is possible by aspiration or inhalation of infected amniotic fluid in utero.

In reviewing the literature it is found that there is much debate on the question of which cases reported should be classified as true congenital tuberculosis. The explanation of such widespread disagreement probably lies in the fact that there has been no definite accepted definition of congenital tuberculosis. We would like to suggest that the following definition of congenital tuberculosis become generally accepted: "Tuberculosis in which the infection occurs before birth by way of the blood stream or by aspiration or ingestion of infected amniotic fluid in utero."

Those cases which result from aspiration of infected material at the time of birth might well be termed "tuberculosis neonatorum."

The first authentic case of congenital tuberculosis in the human being was reported in 1891 by Schmorl and Birch-Hirschfeld.² Since that time many others have been reported.

In 1914 Pelm and Chaliere,³ made an extensive study of congenital tuberculosis and accepted only fifty-one cases as definitely proved.

In 1922 Whiteman and Greene⁴ reviewed the literature and found 113 authentic cases and 519 more or less doubtful cases. To these they added their own case and several others they found in the literature.

Horak⁵ in 1927 stated that the literature revealed 114 authentic and 519 doubtful cases of hereditary tuberculosis.

Beitzke⁶ in 1935 reviewed 100 cases and passed sixty-one as true congenital tuberculosis. His criteria of proof of congenital tuberculosis in the infant were that: (1) the tuberculous nature of the lesions in the infant must be proved; (2) a primary complex in the fetal liver is proof of the congenital nature of the tuberculous changes, since it can have arisen only from tubercle bacilli in the blood of the umbilical vein; (3) if there is no primary complex in the liver, the infection is congenital only if (a) tuberculous changes are found in the fetus in utero or at birth or a few days after birth, and (b) in a child who lives longer than a few days if extruterine infection can be excluded with certainty, the child being immediately separated from the mother and kept in an environment free from tubercle bacilli.

¹From the Department of Pediatrics, Employees' Hospital, Tennessee Coal, Iron, and Railroad Company.

Hughesdon,¹² in 1946, tabulated and classified thirty-five cases of congenital tuberculosis reported in medical literature from 1935 to 1945, inclusive, and added four cases which were observed in a children's hospital in England.

In an editorial¹³ in the *Journal of the American Medical Association*, June, 1947, reference is made to the fact that during the last seventy years, 115 proved cases of congenital tuberculosis have been described in the literature, including both cases in which pathologic lesions were present and those in which only a tuberculous bacillema occurred.

The writer, quoting Hughesdon, points out that infection of the fetus may take place when the mother's tuberculous lesion is minimal or even undetectable by present methods of investigation. He also notes that this is consistent with the view that tuberculous bacillema may occur at any time during a period of activity of an existing tuberculous focus, no matter how small.

Chester A. Stewart, writing in Brennemann's *Practice of Pediatrics*, comments on the French investigators' theory of transplacental transmission of the filtrable tuberculous ultravirus. He refers to the writings of Calmette and associates.⁹ These writers feel that infection by this portal with the filtrable ultravirus may exceed 80 per cent of infants born to tuberculous mothers, and that nearly 60 per cent of the alleged newborn carriers of the ultravirus withstand this infection without immediate harm.

Many reasons for being skeptical as to this means of the transmission of the disease have been advanced by Thompson and Farbisher.¹⁰

Stewart concludes that, for the present, infections in utero with a tuberculous ultravirus probably should be looked upon as an interesting possibility requiring much further study before being accepted as an established fact; and that transplacental infection with either the mycobacterium tuberculosis or the ultravirus stage is probably relatively rare.

Buchanon¹¹ reported two cases of neonatal tuberculosis in 1946, but one of these was not truly congenital.

The reader is referred to the excellent treatise of Conrad¹ for a review of the literature until 1938.

CASE REPORT

CASE 1.—B. G. B., a 3 pound, one ounce, female, premature Negro infant, was born at home at 1 P.M. on June 9, 1946. The delivery was precipitate, the doctor arriving just as the baby was born. A time interval of approximately ten to fifteen minutes elapsed between the birth of the baby and its removal from the mother's room. The placenta was expressed and disposed of, since it was not remarkable.

The baby was admitted to the Employees' Hospital fifty-five minutes after birth, and was at no subsequent time in contact with the mother, since for the remainder of her life the baby remained in an incubator with only trained hospital personnel in attendance. The period of gestation was estimated at seven months.

The only significant finding in the family history was that the mother had been receiving antisyphilitic treatment before the baby was born.

On the initial physical examination the only findings were those of prematurity and some cyanosis of the palms and soles.

The admission diagnosis was: premature newborn infant.

Clinical Course.—Routine measures for premature infants were instituted, and the baby progressed satisfactorily until June 22, 1946, at which time a small abscess was noted on the right arm. This was aspirated on this day and incised and drained a day later. On June 27, the baby passed two stools with gross blood. On the following day she began to have a diarrhea and she passed four to six diarrheal stools a day for a week, some with blood. July 6 the stools were normal.

She was given $\frac{1}{2}$ c.c. crude liver extract intramuscularly on July 2, 3, and 4.

Another abscess was noted on the lateral aspect of the right thigh July 9, from which a small amount of thick, yellow, blood-streaked pus was aspirated. It was then incised and drained. Culture of the pus showed *Bacillus coli*. The abscess drained for twenty-four hours and was reopened on July 12, at which time about two drachms of pus were evacuated. On July 22 the baby began to have diarrhea again and on this day she passed eight soft white stools. The next day, the day of death, she passed ten watery white stools and the abdomen became distended. She died at 7:55 P.M.

As previously recorded, the birth weight was 3 pounds, one ounce. The baby weighed 2 pounds, $15\frac{1}{2}$ ounces, on each of the next four days. On the fifth day she weighed 3 pounds, $\frac{1}{2}$ ounce, and the next day had regained her birth weight. From this time until three days before death her weight gain was steady. On the twenty-second day she weighed 3 pounds, 4 ounces; on the twenty-ninth day the weight was 3 pounds, 9 ounces, and on the thirty-fourth day she weighed 4 pounds. On the thirty-eighth day she weighed 4 pounds, $3\frac{1}{2}$ ounces.

LABORATORY REPORT

Urine.—6/20/46 Negative except for occasional white blood cells.

7/15/46 Negative except for trace of albumin.

Serology.—7/3/46 Negative Kahn.

	Date	Hgb. (%)	W.B.C.	R.B.C.	Differential
Blood.—	6/10/46	80	12,500	4,425,000	J-4, St.-5, P-40, L-47, M-4
	6/27/46	60	13,000	2,700,000	
	6/28/46	55	5,500	2,400,000	
	7/ 1/46	45	6,000	2,200,000	
	7/ 3/46	50	6,000	2,000,000	
	7/ 6/46	40	8,750	1,600,000	
	7/ 8/46	55	9,250	2,500,000	
	7/10/46	55	14,500	2,675,000	
	7/11/46	65	12,500	3,400,000	
	7/13/46	55	17,250	2,225,000	
	7/15/46	55	14,000	2,300,000	E-2, St-14, P-32, L-52
	7/20/46	50	16,250	2,500,000	
	7/22/46	55	21,000	3,325,000	

Exudates.—7/ 9/46 Smear from pus from abscess negative for organisms.
7/11/46 Culture of pus from abscess. *Bacillus coli*.

AUTOPSY REPORT

Clinical Diagnosis.—Acute miliary tuberculosis
Prematurity
Bronchopneumonia
Gastroenteritis, due to unknown cause
Anemia of prematurity
Furunculosis.

Gross Anatomical Diagnosis.—

Purulent bronchopneumonia
Cerebral edema and hyperemia.

This was the body of an emaciated Negro female infant, 47 cm. long. The arms and legs were very thin. The pupils were round and even, being 4 mm. in

diameter. There was a clear fluid exuding from mouth and nose. No abnormalities of development were noted. The abdomen was greatly distended and tympanitic. The external genitalia were those of an infant female.

Peritoneal Cavity: The intestines were greatly distended with air. The viscera had its normal relationship. The liver was slightly below the right costal margin. The diaphragm was at the fifth rib, bilaterally.

Pleural Cavity: The lungs were voluminous, with smooth glistening surfaces. No adhesions were noted.

Pericardial Cavity: The surfaces were smooth and glistening, with a few cubic centimeters of dark yellow fluid present.

Heart: The heart was normal in size, with small petechiae over the epicardial surface, especially around the coronary sulci. The myocardium was dark grayish brown, with increased fragility. The foramen ovale was anatomically patent, but physiologically closed. The ductus arteriosus was only a strand.

Lungs: Both were well filled with air, having a light pink color. On section the bronchi were filled with a light yellow puslike material that may or may not be purulent material. There did not appear to be a great deal of increased peribronchial fibrosis. The substance was pink, moist, and had a bloody fluid oozing on the cut surface.

Liver: Appeared slightly enlarged with rounded edges. The substance had a dark reddish brown color with green mottling. These small green areas on the cut surface appeared to be especially prominent in the central zone of the lobules. The gall bladder and common duct were natural.

Spleen: The spleen was normal size, having a deep brown color with the lymphoid bodies readily seen.

Adrenals: Did not appear significant.

Kidneys: Both were of normal size, showing markedly a fetal lobulation. The bladder and ureters were normal.

Gastrointestinal Tract: The bowels were distended with air. The stomach and small intestines contained undigested and clear watery fluid. There were numerous petechial hemorrhages within the mucosal wall. The fluid of the lower intestines and colon took on a hemorrhagic tint.

Brain: There were numerous small areas of hemorrhage beneath the raised scalp. The tentorium cerebelli was a deep purple with small hemorrhagic areas over it and adhesive bands with the overlying brain tissue. Several small lacerations were seen. The configuration of the cerebrum was flattened and edematous, with the vessels being engorged. Several small hemorrhages were noted. An especially marked area of engorgement was seen over the cerebellum with a large hemorrhage over its left pole.

Microscopic.—

Heart: Pericardium, endocardium, and myocardium were negative.

Lungs: Areas of the lung showed multiple tubercle formations. In the center of these tubercles there were pyknotic nuclei and hyaline caseation. Around these centers were epithelioid cells. The cellular reaction around the tubercle was mostly monocytic, but lymphocytes and a few neutrophils were seen. Occasional giant cells were present. The picture was suggestive of active tuberculosis. Acid-fast stains were positive for acid-fast bacilli.

Liver: A few small areas of focal necrosis were seen. The Kupffer cells of the sinusoids were loaded with red cells.

Small Intestine: Negative.

Spleen: The section showed two tubercle-like lesions. One consisted of a central area of acute inflammatory cells surrounded by epithelioid cells; the other was a solid mass of epithelioid cells and monocytes. A giant cell was seen near its center.

Kidneys: Negative.

Microscopic Diagnosis: Active tuberculosis of lungs, spleen, and possibly liver.

Clinical Summary.—This patient was a premature infant born at the seventh month of pregnancy. She cried immediately after birth and was brought to the hospital at once. She was a small child, and was given oral plasma, water, and Dextri-Maltose. A small abscessed area on the right thigh was noted, opened, and drained. On July 23, 1946, the abdomen became distended and soda enema was given. She died the following night at 7:55 P.M.

(We wish to express our thanks to Drs. J. A. Cunningham and L. C. Posey for doing the necropsy.)

CASE 2.—M. E. B. was the mother of B. G. B. This 19-year-old Negro primipara was admitted to the hospital on June 25, 1946, with complaint of chills, fever, and foul vaginal discharge. Sixteen days prior to admission she was delivered of a premature infant by precipitation. Post-partum convalescence was uneventful except for a bloody discharge until four days prior to admission. At that time she began to have backache, headache, chills, and fever, and the vaginal discharge became yellow and foul smelling. At the onset of these symptoms she was seen by a physician who gave oral penicillin without results. She was sent to the hospital for diagnosis and treatment.

Past History.—The past history was negative except for a positive Wassermann found in prenatal clinic. A presumptive diagnosis of syphilis was made and she was treated in the Anti-Luetic Out Clinic. The family history was negative.

A review of systems revealed poor appetite but no nausea or vomiting, no cough or chest pain. There was no bowel disturbance and no urinary difficulty.

Physical Examination.—Temperature 104.6° F., pulse 120, respiration 20, blood pressure 120/70. An undernourished, underdeveloped, Negro female, lying quietly in bed not appearing acutely ill. Eye, ear, nose, and throat examination was negative. Chest was clear to percussion and auscultation. Heart rate and rhythm were regular. No murmurs or enlargement were noted. The abdomen revealed no tenderness or masses. Pelvic examination revealed a foul discharge but no other pathology.

Clinical Course.—The clinical course was marked by daily spiking fever from 104° to 105° F. Treatment was symptomatic and supportive. She was given 25,000 units of penicillin, intramuscularly, every three hours for 1,000,000 units, without apparent result. An x-ray of the chest on the sixth hospital day was reported: "Extensive generalized miliary pulmonary infiltration, compatible with acute miliary tuberculosis." A Mantoux test on July 4, 1946, was negative. A check plate of the chest two weeks after the first showed extension of the miliary process.

The patient continued gradually downhill with daily spiking fever, and expired on the twenty-first hospital day. Permission for autopsy was refused.

LABORATORY REPORT

Urine.—Catheterized specimen on admission showed two plus albumin, one plus pus and an occasional cast.

Blood.—6/25/46 Hgb. 60 per cent, R. B. C. 3,250,000, W. B. C. 5,500, P-60, J-15, L-25.

6/25/46 Smear for cell pathology, anisocytosis, poikilocytosis, and central achromia.

Sputum.—Sputum was negative for tuberculosis on four occasions. Sedimentation rate corrected was 37 mm. per hour.

Blood Chemistry.—Blood sugar 70 mg., nonprotein nitrogen 19 mg., creatine 0.8 mg.

COMMENT

We feel that this case represents true transplacental transmission of tuberculosis, since the mother was a young Negress who, before delivery, and for a period of about two weeks post partum, had no history or findings suggestive of tuberculosis; and who even during her final illness had a negative Mantoux and negative sputum on repeated examinations, but during her last illness presented a characteristic chest x-ray and clinical picture of acute fulminating miliary tuberculosis. The rapidity with which the disease disseminated in the mother explains her lack of reaction to the intradermal injection of tuberculin.

The contact between mother and baby was minimal and besides this, miliary tuberculosis is considered to be noncontagious.

Most case reports of congenital tuberculosis are on mothers who were in advanced stages of the disease of the "adult" or open type, and many of the cases of tuberculosis in the offspring were due to infection at the time of birth from aspiration of infected material in the birth canal at the time of delivery.

SUMMARY

1. A brief review of the literature on congenital tuberculosis is presented.
2. One case of transplacental transmission of tuberculosis is reported.

CONCLUSIONS

It is suggested that the following definition be accepted generally for congenital tuberculosis: "Tuberculosis in which the infection occurs before birth by way of the blood stream, or by aspiration or ingestion of infected amniotic fluid in utero," and that all cases occurring at birth by the aspiration of infected amniotic fluid or tuberculous material present in the birth canal be classified as "tuberculosis neonatorum."

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CEREBELLAR MEDULLOBLASTOMA IN A SEVEN-MONTH-OLD INFANT

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CLEVELAND, OHIO

ATTENTION is called to this case because of the early age at which cerebellar medulloblastoma was seen. The term medulloblastoma was first used by Bailey and Cushing¹ in a classification of gliomas on a histogenetic basis. The undifferentiated cell seen in this type of tumor, first described by Schaper in a series of papers from 1894 to 1897, was named "medulloblast" by Bailey and Cushing.

From a study of human embryos, Kershman² found that the medulloblast is a cell peculiar to the developing cerebellar cortex, in keeping with the observation that medulloblastomas occur exclusively in the cerebellum. With the cell found in the developing cortex, an early age incidence of medulloblastomas would seem likely.

Classification of medulloblastoma is criticized by Stevenson and Eehlin,³ who believe that some should be termed "granuloblastomas" since they are derived from the granular layers of the cerebellum. Of thirty-nine cases of medulloblastoma reported by Cushing⁴ from 1913 to 1926, twenty-four were in patients under 15 years of age with an average age incidence at 10 years. In Cushing's report in 1930⁵ of sixty-one cases, the youngest patient was 2 years of age, but had had symptoms for nine months. Among 4,563 necropsy records reported in 1923 by Wollstein and Bartlett,⁶ there were five cerebellar neoplasms. A diagnosis of glioma (astrocytoma) was made in these patients with ages 2 years, 3 years, 17 months, 16 months, and 13 months, respectively.

Marion's case⁷ of a 16-month-old male with a tumor in the region of the thalamus was reported to be a glioma.

Ford and Firor⁸ reported a case of an invasive tumor covering the base of the brain and extending into the fourth ventricle in a 15-month-old male. The tumor was composed of irregular, spindle-shaped cells with scanty cytoplasm and definite glia fibrils.

Canavan and Hemsath⁹ described a small body made up of ependymal cells in the floor of the fourth ventricle of a premature infant who died a few hours after birth.

Cases of teratomas, cysts of the choroid plexus, tumors of the pineal region, sarcomas, ependymomas, and papillomas have been reported in very young infants.

Gross¹⁰ reported an 11-month-old male with symptoms since 10 months of age, who had a cerebellar tumor closely resembling a medulloblastoma. Gross also reported two other patients with conditions diagnosed as medulloblastoma; the patients were 17 and 19 months old, respectively. The average age of twenty-five patients reported by the Association for Research in Nervous and Mental Diseases¹¹ in 1937, was 19 years; the youngest patient was 4 years and the oldest 50 years of age.

CASE REPORT

A 7-month old white male was admitted to the Babies and Childrens Hospital of Cleveland with the chief complaint of irritability, left facial paralysis, and turning of the head to the left. Birth history was normal and family history was noncontributory. He had been a healthy, normally developing infant until 6 months of age, when he began holding his head to the left side. From that time the infant had vomited projectilely about once a

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day. The vomitus did not contain bile. At 6½ months of age a gradually increasing left facial paralysis was noted, together with general irritability. There had been no significant fever. The mental development to the time of onset of his illness had been normal.

Findings at physical examination on admission were: temperature, 37.6° C; weight, 7,010 Gm.; head, 41 cm., chest, 12 cm., a very irritable 7 month old white male, head held to the left side with rotation of 15 degrees to that side. The infant tended to assume an opisthotonic position. The anterior fontanel bulged slightly and was quite tense. There was marked weakness of left facial muscles (seventh nerve) with diminished sensation on that side (fifth nerve). Pupils were equal and regular, and reacted to light. A weakness of the left external rectus muscle (sixth nerve) was noted. The left corneal reflex was diminished (fifth nerve). Fundi: papilledema was moderate bilaterally but somewhat more marked on the left. Marked resistance was observed to anterior flexion of the neck. The tongue was deviated to the right (twelfth nerve), and the gag reflex (ninth nerve) was questionably diminished. The uvula did not deviate. All deep tendon reflexes were hyperactive.

A lumbar puncture was done with caution to avoid possible herniation of the brain stem into the foramen magnum. Spinal fluid was slightly xanthochromic under increased pressure (470 mm.) with 120 lymphocytes and 2 polymorphonuclears. Sugar and chlorides were normal. Admission chest film was interpreted to show a bronchopneumonia in the right hilus. There was no significant change in this film one month after admission. Skull films were normal at admission. Penicillin, intramuscularly, was given for the first hospital days to avoid intercurrent infection and also on the basis of the initial chest film.

It was felt that there was a space occupying lesion of the left cerebellopontine angle which was increasing in size and was subject to hemorrhage. On the second hospital day a spinal fluid contained 1,650 fresh red blood cells per cubic millimeter, 11 polymorphonuclears, 30 small monocytes, and 45 small histiopluc cells. These cells were in "clusters with irregular nuclei and were not inconsistent in size and shape with those found in a medulloblastoma," according to Dr. H. Z. Lund, pathologist. A subsequent spinal fluid specimen showed these cells, while ventricular fluid did not.

At this time Dr. C. S. Beck recommended x-ray therapy in view of the location of the tumor, presence of fever, and age of the infant.

On the fifth hospital day burr holes were made and repeated ventricular taps were made to relieve the increasing intracranial pressure until the twenty-sixth hospital day. X-ray therapy from the fifth to the thirty-first hospital day consisted of a total of 2,000 R. to the left occipital and 1,500 R. to the right occipital regions. At the end of this course of therapy there was considerable skin reaction in the occipital region which delayed operation until the fifty-third hospital day.

During the course of x-ray therapy when the infant was also receiving ventricular taps (in the beginning twice a day) the temperature fell from 39 to 40° C to normal, irritability decreased as did the vomiting. There was no progression or regression of cranial nerve findings. After the course of x-ray, the infant's general course was downhill until the time of operation.

At operation, performed by Dr. Beck, the right cerebellar lobe was found to be displaced to the right with a cyst of the vermis containing about 30 cc of yellow fluid. The cyst extended laterally on the left, extending into the left cerebellar hemisphere and between the hemisphere and brain stem. The wall was very necrotic, part of the roof of the cyst was removed for study while about 15 cc of remaining necrotic material was removed.

For a few days following operation the infant did well, but in a short time his condition became critical and he expired on the tenth postoperative day (sixty-third hospital day). At this time measurements were: head, 46.5 cm.; chest, 36.5 cm.

Pathologic diagnosis of the surgical specimen was "necrotic tumor of cerebellum probably glioblastoma multiforme" according to Dr. H. T. Karsner.

It was felt that accurate diagnosis could not be made, due to the extensive necrosis of the specimen probably as a result of x-ray treatment.

Permission was obtained to remove the brain post mortem through the surgical incision. Microscopic diagnosis of this specimen was consistent with the early clinical impression of cerebellar medulloblastoma.

The tumor was large, necrotic, invasive, malignant, and tended to spread along the pia arachnoid and ependyma. The cells were rather small, somewhat ovoid, having scant cytoplasm and comparatively large, dark-staining nuclei, some of which were round and vesicular, others lobulated, and still others hyperchromatic. Mitoses were frequent. There were abundant vascular channels, many of which were thick-walled arterioles. The tumor cells formed clusters and collars about these vessels giving the so-called "pseudo-rosette" appearance. The tumor was mostly in the pia and arachnoid, and extended for a considerable distance in these linings. The underlying cerebellar tissue in some portions was not unusual, while in other areas there was invasion necrosis, focal hemorrhage, edema, and atrophy. There was marked necrosis in some portions of the tumor. The stroma of the tumor was scant and consisted mainly of pink-staining collagen material.

Interesting features of this case were the occurrence of a cerebellar medulloblastoma in a 7-month-old infant with the tentative diagnosis of the type of tumor made from the examination of the spinal fluid.

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Erratum

In the article by Cohen and Schneck entitled "Natural Incidence of Influenza Antibodies in Children of Different Age Groups" appearing in the February, 1948, issue of the JOURNAL, two paragraphs were moved in type by error. The first two paragraphs on page 159 should follow the first paragraph after Table II on page 156.

Psychologic Aspects of Pediatrics

THE CHILD WITH ASTHMA

RUTH MORRIS BAKWIN, M.D., AND HARRY BAKWIN, M.D.

NEW YORK, N. Y.

IT is unfortunate that a state of mutual suspicion and reluctance to accept each other's role in the study of allergic conditions so frequently exists between the pediatrician interested in allergy and the psychiatrist. Both should be concerned only with the lessons which can be learned through a cooperative, objective study of the conditions which have not responded to ordinary methods of diagnosis and treatment."⁴

The importance of psychologic factors in the pathogenesis of asthma has been recognized since antiquity. This viewpoint was accepted without question until the early years of this century. Since then attention has been directed toward the allergic component. Within recent years interest in the psychologic aspects of the problem has been revived and a fuller understanding of the interplay between the different mechanisms in the etiology of this harassing disease is being developed.¹

The role of the emotions in precipitating the initial and also subsequent attacks of asthma has been stressed by McDermott and Cobb² and by Rogerson, Hardeastle, and Duguid.³ McDermott and Cobb were able to elicit a convincing history of emotional factors in thirty out of fifty adults with asthma. Seven others were less convincing but strongly suggestive. They felt that, had more time been spent with each patient, psychologic factors would have been found in more cases. Twenty of their patients reported that the first attack was precipitated by an emotional disturbance.

In both adults and children the situations which most commonly induce an asthmatic attack are threatened separation from the mother, rage, and fear.⁴ It is a not uncommon experience to have a mother report that she is afraid to cross her child lest he have an attack, and that the child's attacks are increased under emotional strain.

The importance of suppressed emotion in precipitating an attack of asthma and the subsidence of the attack coincident with release of tension were mentioned by Salter⁵ in 1882, and this observation has been confirmed by many others since then. Salter states that, "The cure of asthma by sudden alarm takes no time. It is instantaneous. The intensest paroxysm ceases on the instant." He cites the history of a patient who was riding to the city to procure medicine to relieve the attack of asthma from which he was suffering. The patient rode slowly since he feared that exercise would exaggerate his symptoms. His horse ran away, and he was surprised to find that his symptoms had subsided completely.

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¹Jensen, R. A., and Stoesser, A. V.: Emotional Factors in Bronchial Asthma in Children. *Am. J. Dis. Child.* 62: 80, 1941.

Lane,⁶ in an account of her own symptoms, mentions that during adolescence, when she had many episodes of weeping, the number of attacks of asthma was less, only to increase later on when she showed better "control." Dekker⁷ writes of a man whose attack of asthma was abruptly terminated when he was frightened by discovering that a Zeppelin was passing over his house. McDermott and Cobb² tell of a woman whose attacks of asthma became worse when she was annoyed by her husband. However, if she became very angry with him and flew into a rage the attack disappeared entirely at once. They suggest, as a possible explanation for the relief of an attack of asthma by strong emotion, the known beneficial effects of epinephrine on attacks of asthma and Cannon's work on epinephrine and the emotions.

The mothers of children with asthma show certain traits and attitudes with great uniformity.⁵ They are usually the dominating force in the home, the fathers being passive. The mothers have been characterized as narcissistic, ambitious for themselves and their children, critical of their husbands, efficient, often earning more to support the family than do their husbands. They show little affection toward husband and children but are conscientious in their duties toward home and family. The children sense the lack of maternal affection and are disturbed accordingly. There may be intense sibling rivalry, sometimes to an extreme degree.

Parental overanxiety is the rule. The parents fear that an attack may be brought on not only by external factors and food indiscretions but by friction at home. They fear night attacks especially. The child himself becomes apprehensive and overanxious, and poor sleeping habits, restlessness, hyperactivity, and distractibility are the result.

The child with asthma has been described as irritable, aggressive, quick to respond, overanxious, and lacking in self-confidence.⁹ According to Balyeat¹⁰ and Rogerson and associates³ the children with allergy are brighter than average. This has not been the experience of Piness, Miller and Sullivan¹¹ who reported the median intelligence quotient of 145 asthma patients to be 103 as compared with 105 for a group of Los Angeles school children selected at random. Children with asthma appear superior because their physical activities are restricted and they are kept indoors in association with adults, from whom they acquire good vocabularies and grown-up attitudes.

The behavior of the child with asthma is characterized by hyperirritability, overactivity, poor sleep, unreasonableness, and temper tantrums. These conduct disturbances are exaggerated before an attack, and improvement in behavior is often coincident with a decrease in the frequency and intensity of the attacks.

The relationship between the mother and the child with asthma is usually abnormally close. The child is overprotected, and his activities are limited as with chronically ill children in general. He is confined to the house unduly, his diet is restricted, and he is shielded from overexcitement. There may be considerable coddling to make up for these deprivations, and the child is pampered and coaxed and bribed to conform to the parents' desires. Health becomes all important.

Most children adjust to this close relationship with the mother by accepting her authority and relying on her to an abnormal degree. They find it difficult to make decisions and, when faced with new situations, an attack of asthma may result. On the other hand, a few children resent parental coddling and restrictions and become antagonistic, disobedient, and resentful. They are fidgety, destructive, and poorly disciplined. They often make poor adjustments in school.

In some instances the child does well when separated from the mother. Freedom from restrictions, free play with other children, and, most of all, separation from the tensions in the home seem to have a beneficial effect. There are less emotional upsets and, consequently, fewer attacks of asthma. Removal from the home is beneficial, probably, not only because of separation from the allergens but because of the substitution of a stable, emotionally healthy environment for the highly charged atmosphere of the home.

Retardation in schoolwork is common and has been considered to be due to frequent absences from school. The child may be placed in a class with younger children, which makes social adjustment difficult. A certain number of children with asthma have a specific reading difficulty. Though this does not appear to be more frequent than in school children in general, it usually goes unrecognized since the reading disability is attributed to the numerous absences from school.

The personality and behavior problems of the child with asthma are understandable as reactions to the parental personalities and attitudes. It is to be expected that the child will react to parental overanxiety, oversolicitude and overindulgence with immature and demanding behavior.

It has been suggested that the behavior disturbances of some children with asthma may be accounted for by local edema within the cranial cavity.¹² The resulting increased pressure may cause headache, vomiting, and dizziness. The child with asthma becomes irritable and disagreeable during a seizure. When the offending agent is removed, the child's mental attitude returns to normal. Dees¹³ observed electroencephalographic changes in a large number of children with asthma, which tended to become normal with control and improvement of the allergy.

The extent to which emotional factors influence the severity of the asthma varies considerably. In some children they dominate the picture; in others their influence is minimal. The relative importance is estimated on the basis of careful history-taking and clinical observation of the mother and child.

History-taking should include information on the relation of emotional episodes to the occurrence of an attack; the child's and the parents' attitude toward an attack; the interparental relationships and the personalities of the parents, especially the mother; the parental attitudes toward the child, with especial reference to oversolicitude, overindulgence, overanxiety, and rejection; the personality make-up of the child, especially as to anxiety, immaturity, dependence; the relation to the siblings; the amount and nature of restrictions on physical activity; the relation to school.

By way of management, an attempt should be made to free the mother of her anxiety by reassuring her as to the benign outcome of the attacks. The ill effects of overindulgence on the personality development of the child as well as on the frequency of attacks should be stressed. Free activity and a full diet should be permitted as far as is compatible with the child's health. Rigid supervision should be relaxed, and the child should be allowed to make decisions compatible with his developmental status. Regular attendance at school should be urged, and difficulties at school should be corrected by special training if necessary. An attempt should be made to relieve tensions in the home.

Where the emotional difficulties in the home are deep seated, the aid of a psychiatrist should be enlisted.

Attention to the emotional and situational problems of the child with asthma in no way precludes other forms of therapy.

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Comments on Current Literature

INTRAVENOUS ADMINISTRATION OF FAT

VARIOUS discussions of parenteral alimentation have stressed repeatedly the need for a more efficient means of meeting energy requirements. In summarizing studies on infant diarrhea, Gamble¹ has pointed out that "the infant's food provides only a small surplus of oxidizable substances above the requirements for energy expenditure needed for growth. Even a small reduction of uptake of these substances will therefore cause progressive depletion of the energy stores of the body." Data are presented which give these simple and evident physiologic propositions quantitative illustration. Taking into consideration the difficulties encountered in attempting to satisfy energy needs by parenteral route, Gamble concludes that "the great desideratum would seem to be fat in such form that it can be given parenterally," and expresses the hope that "current attempts to produce a preparation of fat which will serve this end will go forward successfully."

In a recent issue of the *British Medical Journal* (Jan. 3, 1948), Magee² reviews the subject of intravenous alimentation. He concludes that, despite major advances in this field, energy requirements cannot be met readily by the usual methods of parenteral therapy and that the energy problem is one of incorporating fat into the injections in usable form. Magee describes work by Ivy, the results of which were made available to him by personal communication. Ivy succeeded in preparing a stable emulsion with which he was able to keep dogs in nitrogen balance, constant weight, and good health for forty-two days by exclusive intravenous feeding. This emulsion is composed of refined butter oil, purified lecithin, a sorbitan wetting agent ("Span 20"), glucose, and sodium cholate. Details of preparation are given in Magee's article, which states that while it has not been possible as yet to prepare a fat emulsion satisfactory for human use, "the work of Ivy and his colleagues is an important step in that direction."

Of special interest in this connection is an article by Shafiroff and Frank³ in *Science* (Nov. 14, 1947) entitled, "A Homogeneous Emulsion of Fat, Protein and Glucose for Intravenous Administration." In a brief descriptive review of the various types of emulsions, reference is made by these authors to the use of egg lecithin, soybean phosphatides, and other agents used as stabilizers in the emulsification and stabilization of fat. However, while such emulsions have been well tolerated in some cases, they have not proved uniformly dependable because of varying degrees of toxicity of the stabilizing agent. Other methods of stabilization, such as the use of hydrophilic colloids, were discarded experimentally because of the frequency of fatal embolism.

In the laboratory of experimental surgery at New York University College of Medicine, two satisfactory types of fat emulsion have been prepared, the first an emulsion of coconut oil and serum albumin which on homogenization yielded a highly stable preparation well tolerated intravenously; the second derived from glucose, protein, and a neutral saturated coconut oil which could be sterilized with safety. The basic proportions of these constituents are as follows: "one l. of 6 per cent infusion gelatin (Knox P-20), one l. of protein hydrolysate 5 per cent amino acid solution, 200 c.c. of 50 per cent glucose solution, and 100 grams of pure, refined, edible coconut oil."

"After thorough mechanical agitation, the mixture is put through the Logeman homogenizer, an instrument so constructed as to make possible sterilization of its working parts. After this procedure of emulsification and homogenization, the material is collected in sterile vacuum bottle dispensers without any other processing and stored in the refrigerator. Refrigeration converts the emulsion into a solid gel which can be restored to the liquid state by warming the dispensing flask in hot water. Refrigerated samples have maintained complete stability after two months' storage: Test samples of the pH of the emulsion averaged 6.5. The droplets were smaller in size than that of the canine erythrocyte and were comparable to that of the chylomiera. The concentrations of fat, protein, and glucose were approximately 5 per cent each and averaged 800 cal./l. The gelatin acted as a stabilizer, partially as a source of nutrient energy, and served to maintain colloid osmotic pressure."³

This emulsion was administered intravenously to seven dogs and to twelve hospital patients. Three patients in the postoperative period were maintained exclusively on this emulsion with satisfactory results. One malnourished patient received intravenously with benefit a total of 5,500 c.c. of the emulsion (approximately 200 Gm. of fat) over a period of eight days. No thrombosclerotic changes were noted in the recipient vein, and the preparation was not irritating when infiltrated into the tissues. In dogs studied at varying intervals following the administration of this emulsion, no evidence of fatty degenerative changes was noted in liver, lung, brain, or other organs.

This brief report concerning the possible use of a homogeneous emulsion of fat, protein, and glucose for intravenous administration in human subjects offers promise of real advance in this important field. Clinicians will await with interest more detailed studies concerning utilization of fat administered in this manner and more extensive reports of clinical application.

RUSSELL J. BLATTNER.

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Communication

To the Editor:

The Hungarian Medical Trade Union desires to celebrate the centenary of the Liberty War by arranging a medical convention in Budapest between Sept. 4 and 12, 1948. In the course of this week, the Pediatric Section will organize an International Congress of Pediatrics.

Of the five days of the Congress, two will be devoted to plenary sessions of all the sections. On three days the following topics will be discussed: rheumatic fever, toxicosis, and social significance and results of pediatrics. Lectures on miscellaneous subjects will also be held.

All pediatricians interested in the Congress are invited to participate. Those who expect to attend the Congress should communicate with the Centenary Congress Committee, Bokay János u. 53, Budapest 8, Hungary. Those who wish to take part in the discussion of one of the main topics or to present a paper on another subject are requested to give the title and a short summary of their lecture.

PAUL KISS, M.D.

PETER V. VÉGHÉLYI, M.D.

News and Notes

The American Board of Pediatrics announces the following examinations for 1948:

Cleveland, April 23, 24, 25

Chicago, June 25, 26, 27

Seattle, September 10, 11, 12

Atlantic City, November 17, 18, 19

Including those who passed the examination in Philadelphia in January, 2,749 certificates have been issued by the Board. The first certificate was dated June 10, 1934.

The annual meeting of the Society for Pediatric Research will be held on May 4 and 5, 1948, at the Seaside Hotel, Atlantic City, New Jersey.

The incidence of the infectious diseases common to children was low in 1947 throughout the United States, according to figures for the year through the week ending December 27, appearing in the Public Health Reports. Some of the figures are as follows:

	1947	1946	5-YEAR MEDIAN 1942-1946
Diphtheria	12,511	16,194	15,559
Measles	215,719	662,972	602,085
Scarlet Fever	83,300	112,981	140,475
Polio myelitis	10,808	25,264	13,731

Whooping cough had an increase in reported incidence with 153,805 cases against 100,212 in 1946 and a five-year median of 123,554. Measles was definitely on the increase during the last few weeks of the year.

The U. S. Army Medical Corps now has a number of positions open in Army hospitals in Germany and Austria which can be filled by physicians who have completed their formal board requirements (residence phase) but who need one or two years of practice limited to their specialty. As of Jan. 1, 1948, there were ten positions available in pediatrics. These hospitals are registered with the A. M. A., and vary in size from station hospitals of 150 beds to general hospitals with 1,000 beds. This training may be acceptable by the specialty board as part of the period usually required to be spent in limited practice and experience prior to admission for examination. Interested members of the medical profession who have completed the formal training requirements for certification in one of the special fields are eligible to apply for these positions.

The locations provide excellent facilities and equipment, a wealth of clinical material. and the services of visiting consultants who are outstanding specialists in the various fields of medical practice.

The applicant may avail himself of this training for periods of one, two, or three years. Those applicants who are selected and who hold reserve commissions in the Medical Corps, will usually be recalled to active duty in the highest grade attained prior to release from previous active service. Those who do not hold such reserve commissions will be tendered a reserve commission in the Medical Corps in keeping with their age, years of professional experience, and prior service in any branch of the Armed Forces. Prior military service is not required. Individuals who are members of the U. S. Naval Reserve must transfer to the Army Reserve before being called to active duty. Families of married applicants will be allowed to accompany them to the place of duty. Suitable quarters are available. Families of individuals who do not declare their desire to serve for periods to exceed one year cannot be transported at government expense.

Eligible physicians are invited to communicate with The Surgeon General, U. S. Army, Washington 25, D. C., for further information. Inquiries should include the following information: name, address, age, nationality, marital status, dependents with age of each, medical school and graduation date, internship and date, details of graduate training, specialty and geographic location desired, contemplated length of service, details of prior military service.

Public Law 365, passed in 1947, makes it now possible for civilian doctors to become commissioned officers in the regular Navy, provided they meet the professional and physical qualifications. This law is unique in that it does away with, for the first time, the age limitation of 32 years and permits doctors in civilian practice to enter the Navy and be commissioned with the rank up to and including Captain. The law considers all strata of the medical profession, as interns, former medical officers who have resigned, and practicing physicians.

Applicants must be citizens of the United States, graduates of a Class "A" medical school, and have served at least one year's internship in an approved hospital. Candidates will be judged on a number of qualifications, such as being a diplomate of a specialty board, teaching connections, number of years of professional practice, hospital or laboratory connections, and military service. The allocation of rank to successful candidates will depend upon their academic age, professional standing, and experience in the medical field. Successful candidates will then be integrated in line with medical officers of the regular Navy. This means that they will be eligible for promotion along with their fellow officers of equal rank.

Doctors interested in such a career should write to the Bureau of Naval Personnel, via the Bureau of Medicine and Surgery, Navy Department, Washington, D. C.

The American Jewish Joint Distribution Committee, 270 Madison Ave., New York, is in urgent need for certain medical personnel for work with the Jews in Europe. The following places must be filled to carry out their program: two qualified public health

physicians; six public health registered nurses, one chief nurse to organize programs; one health consultant capable of setting up training schools for practical nurses; two nurse educators to head these schools; three medical social workers; and two public health dentists. All personnel must enlist for eighteen months. A knowledge of Yiddish is necessary.

The *Société de Pédiatrie de Paris* will meet at 4:30 P.M. on the third Thursday of every month at the Hôpital des Enfants Malades, 149 rue de Sevres. The president is Dr. G. Heuyer, 1 avenue Emile Deschanel, the secretary is Dr. Maurice Lamy, 94 rue de Varenne.

Following is the condensed financial statement of the **Fifth International Pediatrics Congress**:

Receipts

Subsidies from Pediatric organizations in U. S. A.	
American Academy of Pediatrics (U. S. Members only)	\$18,855 00
American Medical Association (Pediatric Section)	3,000 00
American Pediatric Society	1,000.00
Society for Pediatric Research	75 00
Contributions from philanthropic foundations and individuals	40,075.00
Contributions from industry	60,100.00
Revenue from registration fees	55,005 00
Total receipts	\$178,110 00

Expenses

Subsidies to 107 foreign delegates	\$97,061 21
Promotional expenses	2,244.64
Secretarial and office salaries	4,602 36
Printing, stationery, postage, telephone, cables	9,444.52
Bridges	2,430 00
Rental of space	8,000 00
Translations and translation equipment	5,197.98
Exhibit (expenses other than rental)	10,452 92
Reception, teas, luncheon to official delegates	8,000 00
Banquet	16,000.00
Steamer excursion	5,118.84
Post Congress tours	1,836.02
Miscellaneous expenses	7,721.01
	\$178,110 00

The following were certified by the **American Board of Pediatrics** at the examination in Philadelphia, Jan. 9 to 11, 1948:

Dr. Kenneth M. Alford, 159 Bidwell Parkway, Buffalo, N. Y.
 Dr. Edward Buley, 166 19 89th Ave., Jamaica, N. Y.
 Dr. Evelyn J. Basile, 20 8th Ave., Brooklyn, N. Y.
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Book Reviews

The Gifted Child Grows Up. L. M. Terman and M. H. Oden, Stanford, California, 1947, Stanford University Press, pp. 448. Price \$6.00.

What will happen to the gifted child and the child prodigy when he grows up has always been an interesting question. Whether he will adjust to a happy, normal life or will tend to develop neuroses and psychoses under strain, is an important medical question. Will the child superior mentally maintain this superiority when he grows up, or will he fall into the average as far as accomplishments are concerned? Most of us are familiar with what has happened to certain individuals, but the whole cannot be generalized from the particular, and hence the importance of Dr. Terman's study.

To the older pediatricians the name and work of Dr. Terman is well known. To the younger group it may be necessary to explain that in 1925 Dr. Terman published a most interesting study of 1,000 gifted California children. A gifted child was defined as one with an I.Q. of 140 or above. To pediatricians the important finding at that time was that in physical development the gifted children were superior to the general child population.

Follow-up studies of the group were published in 1930, and in the present text Dr. Terman gives data on the group obtained in 1940 and in 1945, when the average age was approximately 35 years. The original group was expanded to 1,528 of whom sixty-one had died. Dr. Terman and his associates have kept in constant touch with the group over the years and secured data on 97.7 per cent of the living in 1940. Over 1,400 of the group were actively cooperating. These figures make it the most remarkable follow-up study we have even encountered. There are hundreds of interesting facts and figures in the book, of which we can present only a few.

Up to 1940 sixty-one had died, or 4.07 per cent. There were ten additional deaths by 1945, including five war deaths. The expectancy figure for the general white population for comparable age is 5.02 per cent. Only six deaths by suicide had occurred, which is below the general rate for age. The insanity rate for the gifted group was 0.91 per cent against an expectancy rate of 1.00 per cent in 1940, and 1.37 against 1.43 per cent in 1945. Most physicians would have expected a higher, rather than a lower, rate. Eighty per cent of the group reported themselves in satisfactory mental health and adjustment.

Educationally, as might be expected, the gifted group were far ahead of the general population. The age of high school and college graduation was at least a year below the California average. Ninety per cent of the men and 86 per cent of the women entered college, and approximately 70 per cent were graduated. Over half the men returned for some form of graduate education as engineering and medicine. The average college grade was high, but for one reason or another, 7.7 per cent of the men flunked out.

Using the Minnesota Occupational Scale for their occupations, 45.44 per cent of the men fall in Group I, professional, and 25.69 per cent in Group II, semiprofessional and highest business. There were 6.22 per cent in Group V, semiskilled and minor business. Of the men, 9.53 per cent became lawyers; 7.59 per cent, teachers; 6.77 per cent, engineers; and 6.08 per cent, physicians. Of the women, 5.4 per cent became teachers of college rank, and 21.1 per cent, teachers below the college level. Two hundred and ninety-nine of the 617 women in the group were employed full time, and 259 were housewives not gainfully employed.

As a whole the earning power of the gifted group was superior to that of college graduates in general of comparable age.

Politically about 20 per cent tended to the radical side, 50 per cent to the average, and 30 per cent to the conservative. There was only one professed "Communist."

By 1945 the proportion of the men and women in the gifted group who had married was definitely higher than the rate for California or the United States as a whole. On the other hand, the offspring rate was lower, with a mean of 1.52 for those married five years or more. By 1945, 14.4 per cent of the men and 16.3 per cent of the women had been divorced or separated. Seventy per cent of these had remarried. The mean I.Q. of 384 offspring given the Stanford-Binet test was 127.7, or decidedly lower than the mean of the gifted parents. However, the number with an I.Q. of 150 or higher was twenty-eight times that for unselected children, upon whom the test is based. The mortality rate for the offspring was very low.

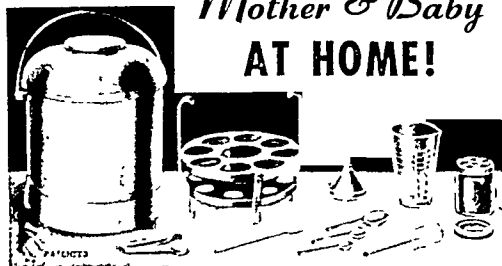
From the study the conclusion can be drawn that the average gifted child by the time he or she reaches 35 years of age has done very well. He is married, happy, physically and mentally sound, and well adjusted to his environment. There is, however, no evidence that the group as a whole has developed outstanding position or leadership. It will be most interesting to find out what has happened at the 45-year age level, as by that time the position and place in life of the individual is pretty definitely fixed. The one striking difference between the gifted group and the general average of human beings at the age of 35 is in the amount of college and university education they have received, and the high percentage in the various professions. This could have been expected, as the very basis of the group—superior intellectual capacity—would lead to intellectual interests and this in turn to the professions as an occupation.

B. S. V.

Traité de Diététique du Nourrisson. Maurice Lust, Paris, 1947, Masson et Cie., pp. 539.
Price 1,000 francs.

In this text Dr. Lust, chief of the Center for Puericulture in Brussels, has assembled an encyclopedic volume on infant nutrition and feeding. There are well over 1,000 references to the literature assembled in the bibliography, including those of 1946, and if the references to the work in other countries are as complete as the knowledge and inclusion of the American work and literature on the subject, there has been very little omitted. The text contains a discussion of maternal and artificial feeding, modified milks, feeding without milk, weaning, and the feeding and nutrition of the premature infant. It is not a text for the student or practitioner, as all the conflicting ideas and thoughts on infant nutrition are presented, but it should be a valuable reference book for pediatric departments for its monumental discussion of the subject and its presentation of the thought and work on infant feeding throughout the world.

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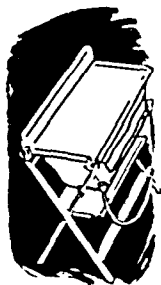
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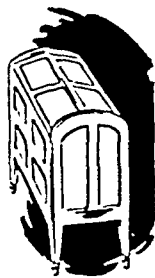
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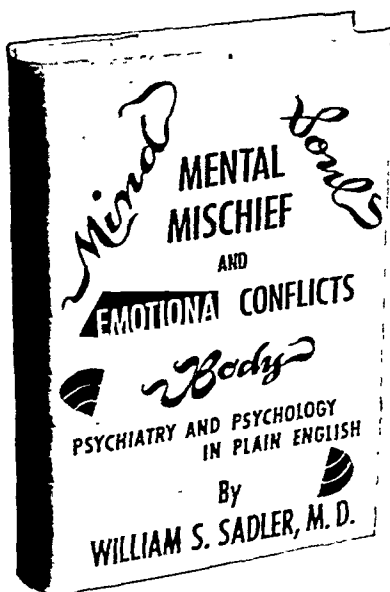
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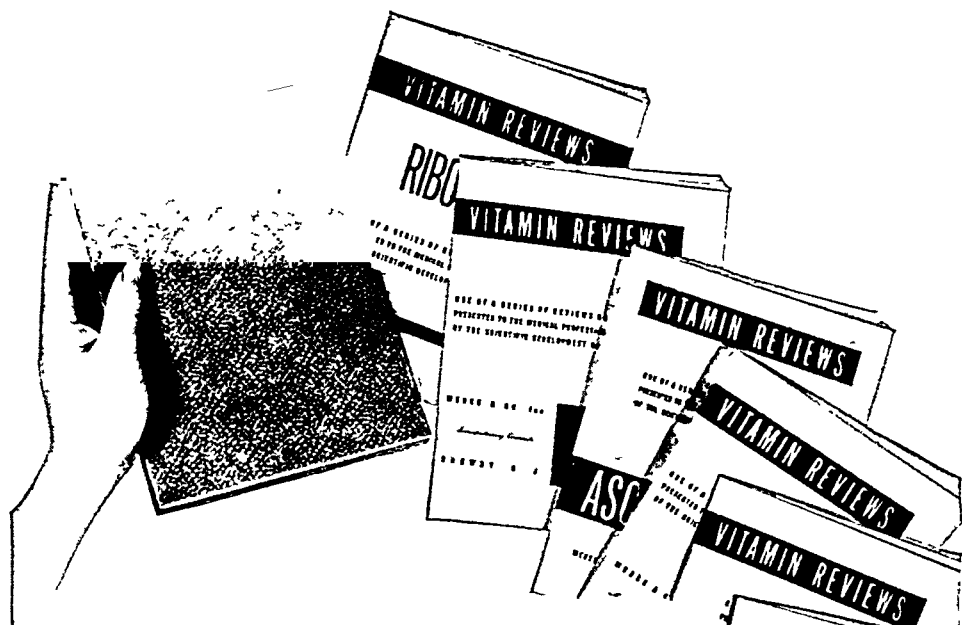


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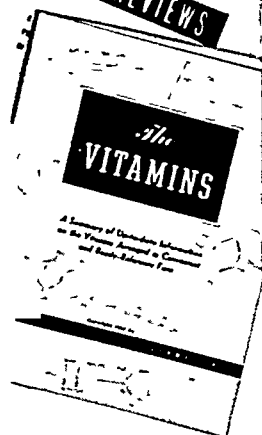
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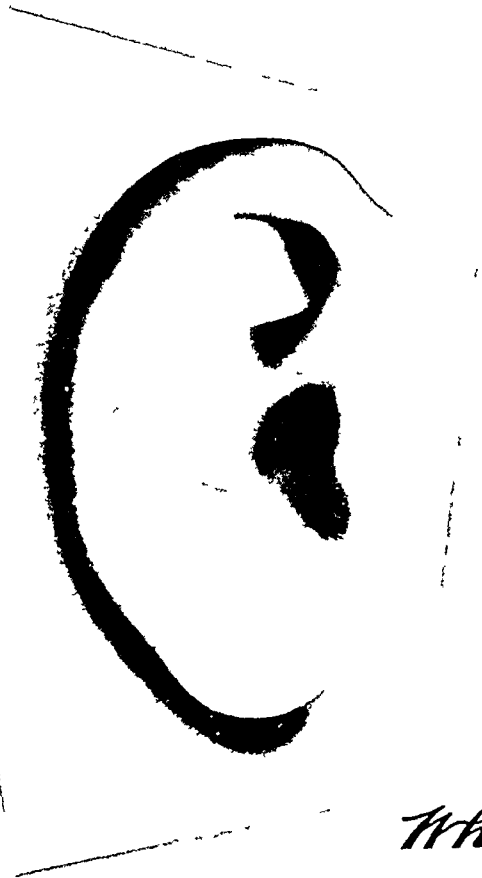
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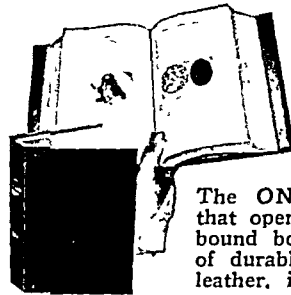
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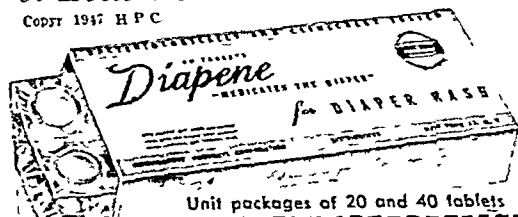
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*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in children between two and fourteen years of age, *Am. J. Dis. Child.* 66:1-11, July 1943.

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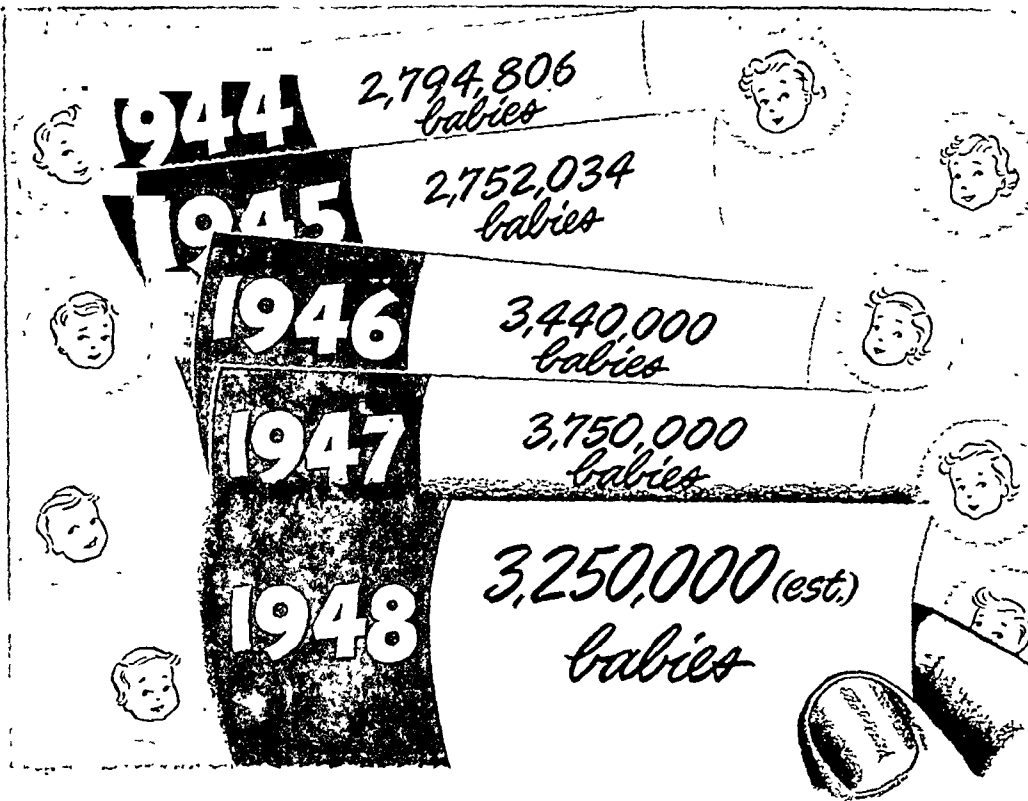
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Vol. 32

FEBRUARY, 1948

No. 2

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS
AND DISEASES OF INFANCY AND CHILDHOOD

CHILD HEALTH CENTER
UNIVERSITY OF MICHIGAN

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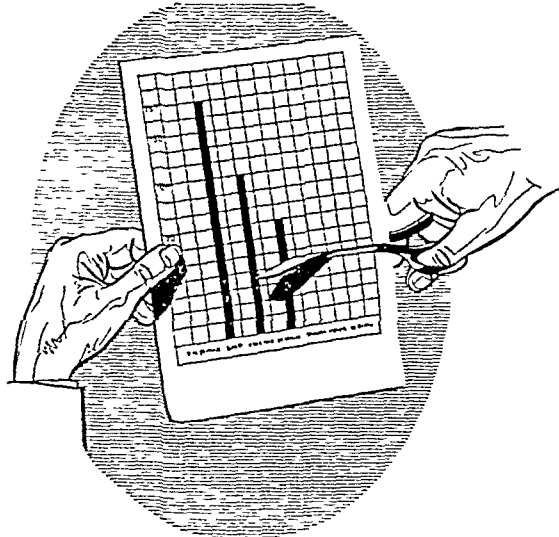
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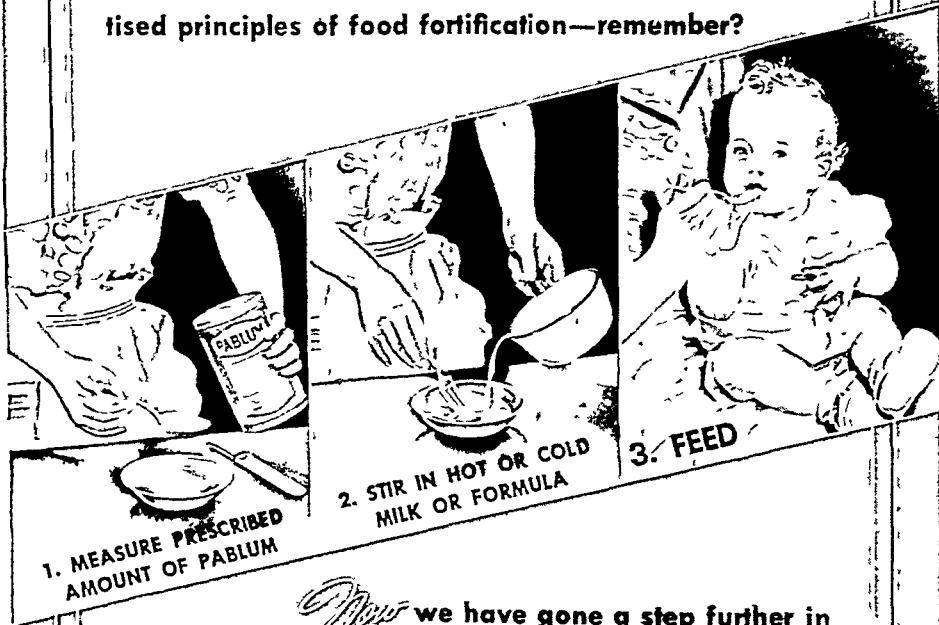
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by

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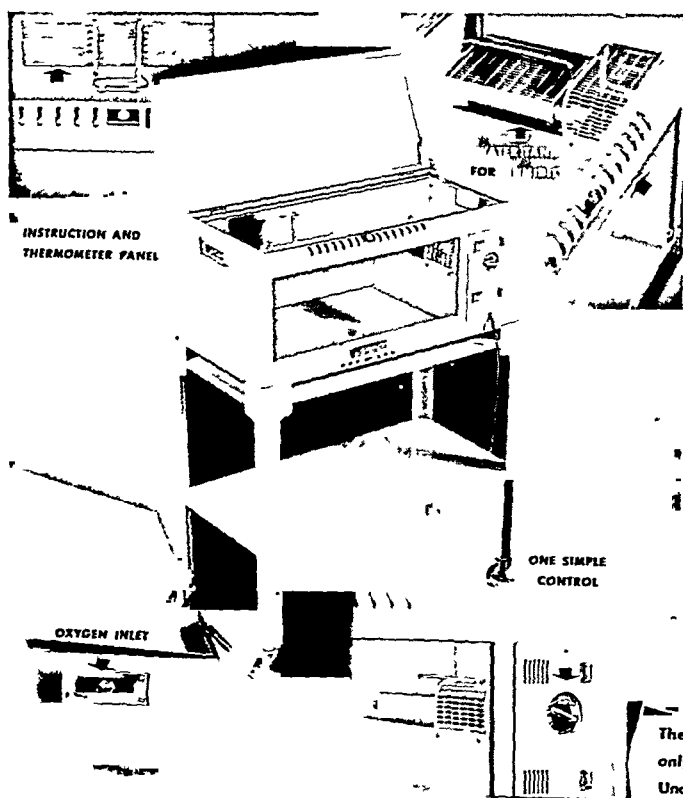
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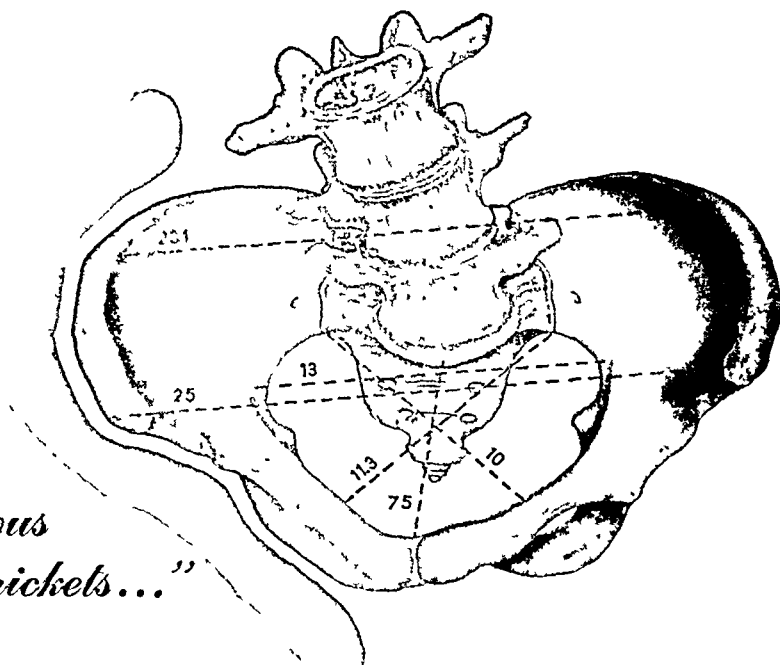
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most serious
result of rickets..."*



In the opinion of many clinicians, "pelvic distortion... is the most serious result of rickets."¹ Severe deformities which "obstruct childbirth and may cause death of both mother and infant"² as well as "the so-called 'simple flat' pelvis"³ are often "rachitic in origin."³ In the prevention of rickets and other vitamin deficiency syndromes, the use of Vi-Penta Drops 'Roche' offers clinically important advantages. The drops are willingly taken even by "difficult" patients since they are miscible and may be added to milk, fruit juice or other foods without significantly affecting the flavor. The comprehensive formula of Vi-Penta Drops supplies in each 10-minim dose no less than 1000 U.S.P. units of vitamin D plus ample amounts of vitamins A, B₁, B₂, C and niacinamide. Vi-Penta Drops are available in 15-cc and 30-cc vials. For a free trial supply, write to department V-3, Hoffmann-La Roche Inc., Roche Park, Nutley 10, New Jersey.

VI-PENTA DROPS 'ROCHE'

T.M.—Vi Penta—Reg U S Pat Off

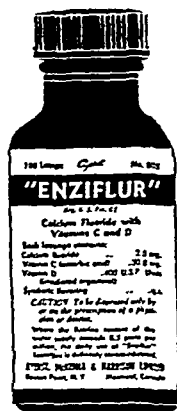
1. F. Bicknell and F. Prescott, *The Vitamins in Medicine*, Grune & Stratton, 1946.

2. M. M. Eliot and E. A. Park, *Brennemann's Practice of Pediatrics*, W. F. Prior Co, Inc, 36 66, 1946

3. J. B. De Lee and J. P. Greenhill, *Obstetrics*, W. B. Sanders, 1943.

HOFFMANN-LA ROCHE INC • NUTLEY 10 • NEW JERSEY

as an aid
in the
prevention
of
DENTAL CARIES



Fluorine therapy in easily controllable form is offered by "Enziflur"
Lozenges, each of which provides 2.0 mg. calcium fluoride,*
30.0 mg. Vitamin C (ascorbic acid) and 400 U. S. P. Units Vitamin D
(irradiated ergosterol). This palatable lozenge should be allowed
to dissolve slowly in the mouth to bring the fluoride bearing saliva
in direct contact with the surfaces of the teeth.
Descriptive literature outlining indications, dosages and
contraindications available to dentists upon request.

*approximately 1 mg. fluorine

"Enziflur" Lozenges (No. 805) are supplied in bottles of 30, 100 and 1000.

AYERST, McKENNA & HARRISON Limited
22 EAST 40TH STREET, NEW YORK 15, N. Y.



Sweetose*

— a major improvement
in corn syrup

—IDEAL CARBOHYDRATE FOR INFANT FEEDING

Sweetose offers many decided advantages both to the physician and to the mother over traditional corn syrups. Made from corn, Sweetose is made under the new acid-enzyme process. The result is a completely new type of corn syrup:



WRITE FOR FURTHER DETAILS

A. E. Staley Mfg. Co.

Box 1091, Decatur, Illinois

Sweetose contains considerably more dextrose and maltose than the older-type corn syrups.

Sweetose is well-tolerated, easily digested and absorbed. The possibility of gastrointestinal upset is minimized.

Sweetose is pasteurized.

Sweetose is easy to use in formulas. Since it has a low viscosity, it will dissolve readily in milk or water at refrigerator temperatures, and thus avoids the stimulation of bacterial growth.

	Representative Analysis of Sweetose White Syrup	Representative Analysis of Ordinary Corn Syrup
Moisture.....	25.2	26.6
Dextrose.....	25.6	14.7
Maltose.....	23.4	13.9
Higher Sugars.....	11.0	13.6
Dextrines.....	8.3	24.8
Sucrose.....	6.3	6.2
Ash.....	0.2	0.2
Available Carbohydrates.....	74.6	73.2
Calories per fluid oz.....	120.0	118.5

No added flavoring or salt.

*"Sweetose" is a trade-mark of the A. E. Staley Mfg. Co. Decatur, Illinois, registered in the U. S. Patent Office.

Announcing

LIQUID PEPTONOIDS

with TERPIN HYDRATE and CODEINE

For symptomatic relief of coughs due to colds



The newest member of *Arlington's* LIQUID PEPTONOIDS* family. It provides the expectorant action of terpin hydrate and the sedative action of codeine phosphate, in the *palatable* LIQUID PEPTONOIDS base so long favored by physician and patient.

Each teaspoonful (5 cc.) represents:

Alcohol (by volume).....	12 %
Codeine Phosphate.....	5.5 mg.
(Warning: May be habit forming)	
Terpin Hydrate.....	17.5 mg.
Chloroform.....	0.3 %
Amino Acids and Polypeptides Derived from Beef, Milk, and Wheat, Equiv- alent to Proteins.....	2.0 %
Carbohydrates: Lactose, Dextrose, Cane Sugar.	

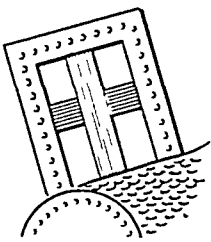
Supplied: Bottles of 4 fl. oz.

For cases in which the action of creosote is desired, LIQUID PEPTONOIDS with CREOSOTE is still available in bottles containing 6 and 12 fl. oz. The physician may thus exercise his choice of preparations in the individual case.

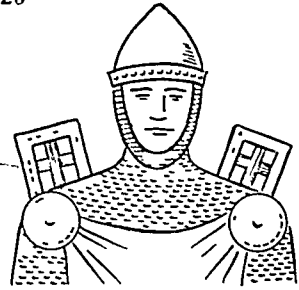
*The word PEPTONOIDS is a registered trademark of The Arlington Chemical Co.

Arlington

THE ARLINGTON CHEMICAL COMPANY, *Yonkers 1, N. Y.*



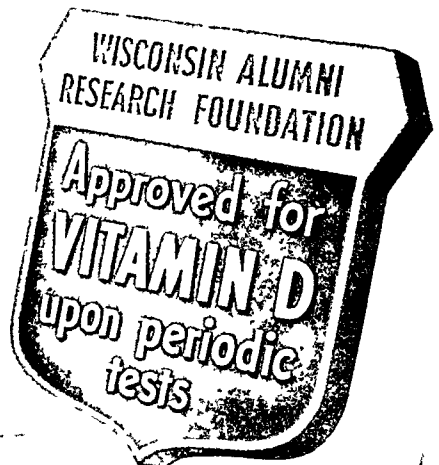
*Armor showing
ailettes. A. D. 1320*



Ailettes, nothing more than plates of forged iron or steel, were worn over the coat of mail to protect shoulders against blows aimed at the headpiece and glancing off.

for extra **PROTECTION!**

JUST as ailettes gave added protection, so does this seal or mention of the Wisconsin Alumni Research Foundation on a product give you extra assurance. For this seal warrants the Vitamin D content. It guarantees that the product is regularly subjected to the Foundation laboratory tests to make certain it meets the high standards and rigid requirements. For almost a score of years the medical profession has advised its patients to "look to the Foundation Seal" with full confidence.



WISCONSIN ALUMNI Research FOUNDATION

M A D I S O N 6 , W I S C O N S I N



IN SUFFICIENT QUANTITY

GLUCO-SULFADIAZINE

Since mixtures of sulfonamides are of apparent advantage, here's a suggestion for "individualizing" therapy to meet the diagnosis in each case... Prescribe a mixture of liquid GLUCO-Sulfonamides (Donley-Evans) of your own design.

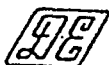
GLUCO-SULFATHIAZOLE

By specifying each liquid sulfonamide to be employed, and quantities, you are assured of the antibacterial activity you desire. Liquid mixtures provide: 1) better protection against renal toxicity, 2) unexpectedly high blood levels in comparison with tablet medication. Donley-Evans' liquid GLUCO-Sulfonamides are the original liquid sulfonamide products containing a sodium lactate-glucose base to maintain an alkaline urine. As single agents, they are more versatile in obtaining therapeutic coverage when used in specific mixtures.

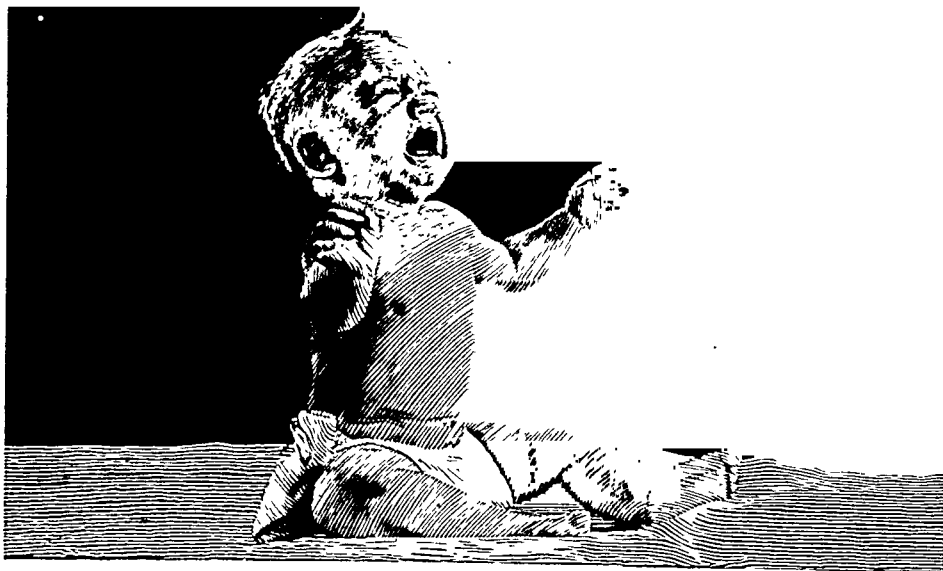
GLUCO-SULFAMERAZINE

GLUCO-SULFANILAMIDE

Supplied: At prescription pharmacies in 6 oz. and pint bottles. Each 5 cc. (one teaspoonful) contains 5 grains of sulfonamide.



DONLEY-EVANS & COMPANY
ST. LOUIS 15, MISSOURI



IMPETIGO responds *quickly* to

Hitherto difficult to control, impetigo has shown dramatic response to Sulfa-Ceepryn Cream—clinical reports indicating that a majority of cases are cleared *within three days*.

Sulfa-Ceepryn Cream provides a rational "three-way" combination of 10% sulfathiazole (antistaphylococcic), 10% sulfanilamide (antistreptococcic), and Ceepryn 1:500 (germicidal detergent).

Ceepryn, having a wetting action that permits quick penetration into the lesion and a bactericidal action that is particularly effective against pyogenic cocci, reinforces the action and widens the range of the sulfonamides. The special water-miscible, vanishing cream base facilitates easy spreading and

Sulfa-Ceepryn

Sulfathiazole, Sulfanilamide and Cetylpyridinium Chloride

Cream

rapid absorption of the active ingredients.

Sulfa-Ceepryn Cream is equally effective in other dermatological pyogenic infections, also adjunctively in varicose, wound, and abscess infections, following surgical drainage. Bandaging is not contraindicated. Complete literature and sample on request.

Sulfa-Ceepryn Cream is available at prescription pharmacies in 1-ounce tubes and 1-pound jars.

Trademarks "Sulfa-Ceepryn" and "Ceepryn" Reg. U. S. Pat. Off.



THE WM. S. MERRELL COMPANY • CINCINNATI, U. S. A.

WALKER

COUNCIL-ACCEPTED VITAMIN DROPS



Potent, convenient, flexible dosage form
Designated for use in pediatrics and geriatrics

VITAMIN C DROPS

Each drop supplies 5 mg. of vitamin C

Supplied in dropper bottles of 15 cc.

CONCENTRATED OLEO VITAMIN A-D DROPS

Each drop supplies 2,000 units vitamin A, 333 units vitamin D

Supplied in dropper bottles of 15 cc. and 60 cc.

Walker

VITAMIN PRODUCTS, INC., MOUNT VERNON, N. Y.

WAITING ROOM TYPES



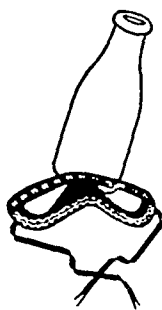
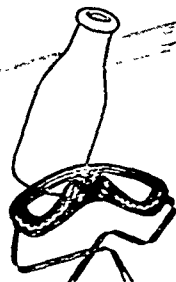
NEW BABY

CAREFUL, DOCTOR, THAT'S JUNIOR TWAMBLY, THE ONLY PERFECT BABY EVER BORN, ACCORDING TO HIS MOTHER. BETTER THINK TWICE ABOUT YOUR ADVICE CONCERNING JUNIOR.

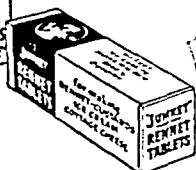
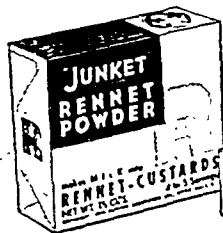
OF COURSE, YOU TAKE NO CHANCE WHEN YOU RECOMMEND "CREAM OF WHEAT" FOR JUNIOR'S FIRST SOLID FOOD. IT'S BEEN TESTED AND PROVED ON SEVERAL MILLION OTHER BABIES DURING THE LAST 50 YEARS, AND JUNIOR WILL THRIVE ON IT, TOO. TELL MRS. TWAMBLY ENRICHED 5 MINUTE "CREAM OF WHEAT" IS SMOOTH, BLAND AND EXTRA NOURISHING. COOKS TO COMPLETE DIGESTIBILITY - EVEN FOR BABIES - IN 5 MINUTES OF BOILING. SUPPLIES LOTS OF IRON AND FOOD-ENERGY, PLUS CALCIUM, PHOSPHORUS, VITAMIN B₁. NO WONDER DOCTORS APPROVE!

"Cream of Wheat" and Chef are Registered Trade Marks and Reg. U. S. Pat. Off.

"make milk a blessing in disguise!"



"JUNKET" is the trade-mark of Chr. Hansen's Laboratory, Inc., for its rennet and other food products, and is registered in the United States and Canada.



When milk is an essential nutritional factor (as in infancy, early childhood, pregnancy, gastro-intestinal and post-operative conditions), and yet it cannot—or will not—be taken by the patient . . . try "dressing up" this dietary "must", with the aid of "Junket" Brand Rennet Powder or Tablets. They make uncooked milk a true blessing in disguise by transforming it (easily and quickly) into appealing, flavorful rennet desserts. Rennet desserts are not only tempting to eye and palate; they retain the nutritional values of milk, yet are more easily and rapidly digested by virtue of the softer, finer, more flocculent curds produced in the stomach by rennin's enzymatic action. "Junket" Rennet Powder is available in six natural flavors, already sweetened; "Junket" Rennet Tablets are supplied unsweetened and unflavored (particularly valuable for diabetics).

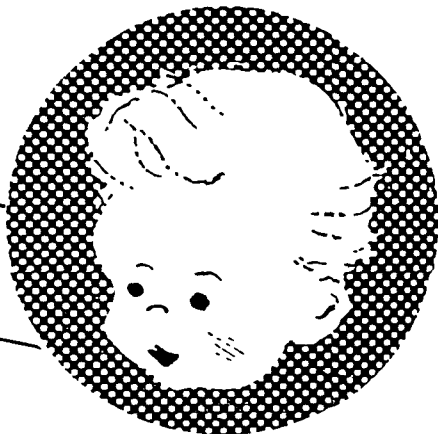
"JUNKET" BRAND FOODS

Division of Chr. Hansen's Laboratory, Inc.
LITTLE FALLS, N. Y.

B-28

when common sense says

**OMIT
SOAP**



In INFANTILE ECZEMAS and DIAPER RASH

TO AVOID EXACERBATION

of infantile eczemas and diaper rash which may occur with soap, and to help prevent these conditions in sensitive babies . . .

USE

LOWILA

COMPLETELY SOAPLESS, GENTLE, EFFICIENT SKIN CLEANSER

LoWILA provides a completely soapless, non-irritant skin cleansing regime; good lather, pH about that of normal skin.

LoWILA Cake superbly mild, no alkali, less slippery allowing firmer hold on baby in bath. Economical.

LoWILA Liquid washes diapers beautifully, gently, without the irritating residue left by soaps. A little goes a long way.

LoWILA is kind to mother's skin too!

Westwood
PHARMACAL CORP.
468 DEWITT ST., BUFFALO 13, N. Y.

WRITE FOR SAMPLE AND LITERATURE
Dept. J.P.

The Journal of Pediatrics



Watch Me "Go"
on
Quaker Oats

Early Feeding of Whole-Grain Oatmeal Helps Promote Baby's Growth*

- * Whole-grain oatmeal leads all natural cereals in Protein.
- * Whole-grain oatmeal contains all ten essential amino acids.

With the development of techniques for determining amounts of individual amino acids in food protein it becomes evident that whole-grain oatmeal not only is higher in protein content than any other natural cereal but the protein is also of higher biological value.

You will find substantiation of these facts in this new booklet:

"Oatmeal's Advantages as a Food for Children"

by Fredus N. Peters Jr., Ph. D.

Director of Research, The Quaker Oats Company

It discusses the nutritional importance of whole-grain oatmeal in the child's diet. Gives some of the latest concepts of adequate nutrition for infants and children. Provides you with handy, quick reference tables which show at a glance the: *Percentage Amino Acid Composition of Food Protein* • *Nutritive Values of Cereal Foods* • *Recommended Dietary Allowances (For children up to 12 years)* • *Vitamin Content of Quaker Oats*.

And contains other useful every day cereal information.

To receive a copy of this helpful book, simply fill out and mail the coupon below. No obligation.

Quaker Oats *Send Today!*

The World's Best-Tasting Breakfast Food



Quaker and
Mother's Oats
are the same

Quaker Oats
Box Q, Chicago 77, Illinois

Please send me a free copy of this new booklet
"Oatmeal's Advantages as a Food for Children."

Dr.....

Address.....

City.....Zone....State.....



★ Completely authoritative ★ Easily understood ★ Profusely illustrated

The Book That Saves Professional Time

So many Pediatricians save their professional time by recommending the Better Homes & Gardens Baby Book to mothers, especially new mothers.

For the BH&G Baby Book gives mothers authentic information and guidance on many routine matters that would otherwise take unnecessary time and attention of the Pediatrician himself. It covers from prenatal to 6 years, with adequate space for recording development from first to eighteenth year.

The BH&G Baby Book was prepared under the guidance of two of

America's eminent pediatricians. In its review, the "Journal of Pediatrics" called it "an excellent book with sound advice, attractively presented, and in keeping with present-day thinking."

The Better Homes & Gardens Baby Book has already proved its value to more than 500,000 mothers—and their medical advisers. It may be purchased at book dealers and infants' shops. If you would like a copy for your own use, have your secretary write for special professional price. Address,

Better Homes & Gardens, Des Moines, Iowa

This Basic Breakfast Pattern...

A Step Toward Better National Nutrition

The widely prevalent habit of skimping or entirely skipping breakfast—prevalent among school children as well as adults—is a major stumbling block in the aim toward improving the nutritional health of America. As a means of combating this practice, a sound basic breakfast pattern has been widely adopted, and is universally recognized as a significant step forward.

This basic breakfast pattern consists of fruit, cereal, milk, bread and butter, and provides an average of 611 calories. The foods comprising this breakfast pattern are widely available and notably economical. If more food energy is required, portions may be increased or other suitable foods such as eggs or breakfast meats may be added.

The cereal serving—consisting of hot or ready-to-eat breakfast cereal, milk, and sugar—is one of the high lights of this breakfast. It provides not only taste appeal and variety, but a well balanced array of essential nutrients. It offers unusual value in this day of increased food costs. The nutrient values of this basic breakfast and the contribution made by 1 ounce of ready-to-eat or hot cereal* (whole grain, enriched, or restored to whole grain values of thiamine, niacin and iron), 4 ounces of milk, and 1 teaspoonful of sugar, are indicated by the table.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association

BASIC BREAKFAST

Orange juice, 4 oz.;
Ready-to-eat or
Hot Cereal, 1 oz.;
Whole Milk, 4 oz.;
Sugar, 1 teaspoon;
Toast (enriched,
white), 2 slices;
Butter, 5 Gm.
(about 1 teaspoon)
Whole Milk, 8 oz.

TOTALS supplied by Basic Breakfast

CALORIES..... 611
PROTEIN..... 20.7 Gm.
CALCIUM..... 0.465 Gm.
PHOSPHORUS . . . 488 mg.
IRON..... 3 mg.
VITAMIN A..... 1074 I.U.
THIAMINE..... 0.52 mg.
RIBOFLAVIN..... 0.87 mg.
NIACIN..... 2.3 mg.
ASCORBIC ACID.. 64.8 mg.

AMOUNTS supplied by cereal serving

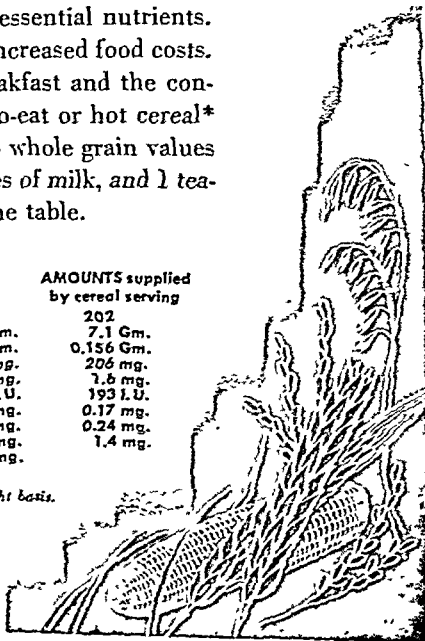
202
7.1 Gm.
0.156 Gm.
206 mg.
1.6 mg.
193 I.U.
0.17 mg.
0.24 mg.
1.4 mg.

*Composite average of all breakfast cereals on dry weight basis.

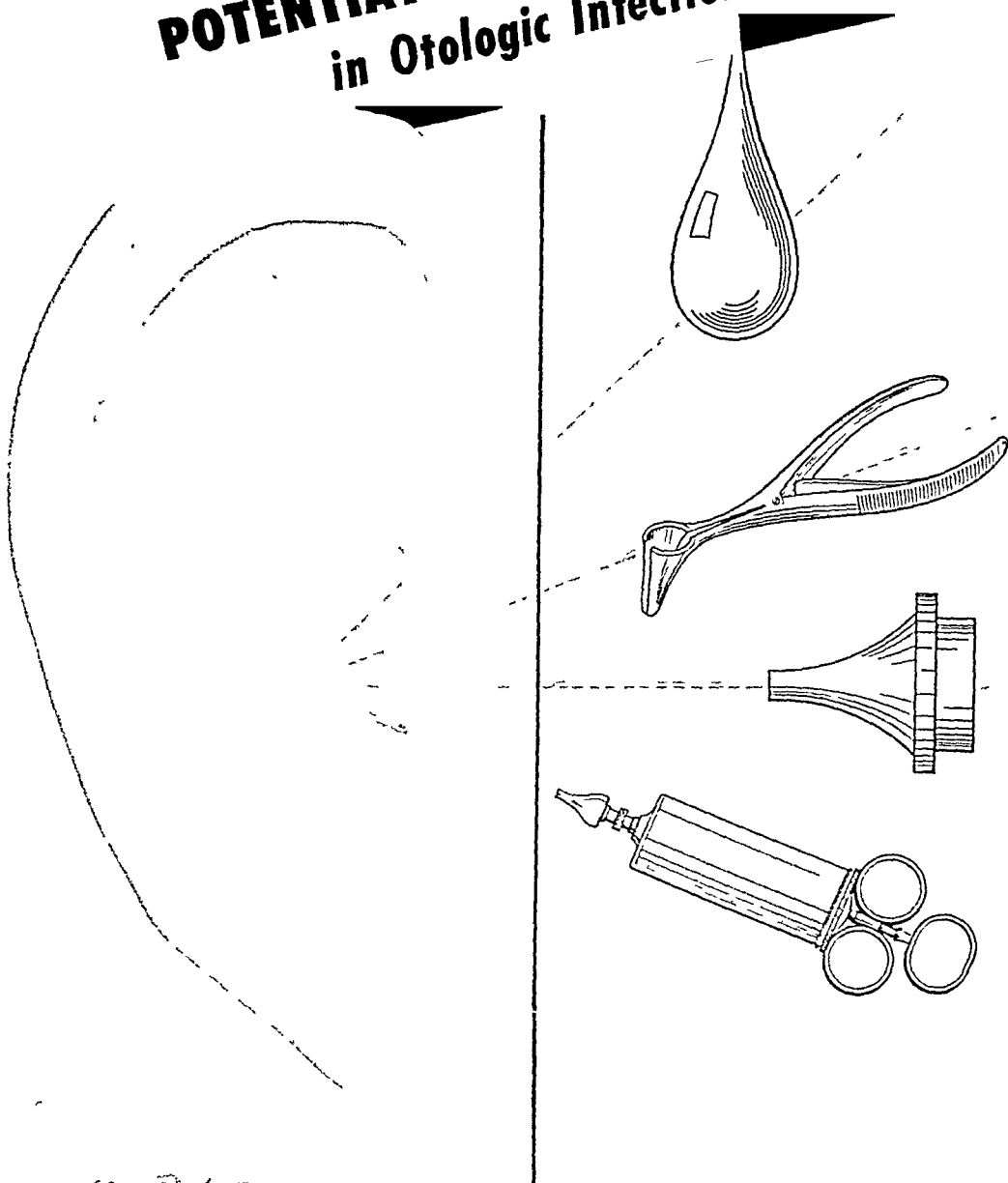
CEREAL INSTITUTE, INC.

A research and educational endeavor devoted to the betterment of national nutrition.

135 South La Salle Street • Chicago 3



ENHANCED EFFECTIVENESS... POTENTIATED CHEMOTHERAPY in Otologic Infections

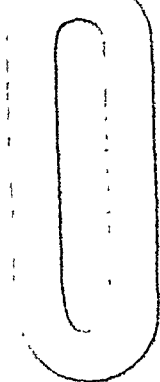


White LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

- 1 **ANALGESIC:** Prompt, effective—without impaired sulfonamide activity.
- 2 **HIGH DIFFUSION:** Penetrates infected tissues without harmful effects to living tissues.
- 3 **PHYSIOLOGICAL DEBRIDEMENT:** Promotes drainage and removal of necrotic debris.
- 4 **POTENTIATION:** Synergized antibacterial potency.
- 5 **WIDE FIELD:** Effective in BOTH acute AND chronic otitis media—fungicidal action in otomycotic infection.
- 6 **ADJUNCTIVE:** A valuable aid to systemic therapy—often reduces need for intensive systemic sulfa medication, thereby averting untoward or toxic reactions.

White's Otomide is composed of 5% Sulfanilamide, 10% Urea (Carbamide) and 3% Anhydrous Chlorobutanol in a specially processed glycerin vehicle of unusually high hygroscopic activity. Supplied in dropper bottles of 1/2 fluid ounce (15 cc.).

White's



tomide

TOPICAL OTOLOGIC CHEMOTHERAPY



UNIQUE In several important respects, Mandelamine is unique among the urinary antiseptics which the physician now has at his command. Mandelamine is safe. It may be confidently administered in therapeutic dosage virtually without consideration of toxic effects, thus eliminating the need for careful selection of patients.

Mandelamine is convenient. The uncomplicated oral administration of Mandelamine requires no supplementary acidification (except in those cases where urica splitting organisms are present), restriction of fluid intake, dietary control, or other special measures.

Mandelamine is prompt and effective. Because of the chemical combination of mandelic acid and methenamine, Mandelamine provides early control and therapeutic effectiveness in common urinary infections. A physician's sample and literature on request.

MANDELAMINE

Reg U S Pat Off
(Methenamine Mandelate)

Mandelamine is supplied in enteric coated tablets of 0.25 Gm. (3 1/4 grains) each, in packages of 120 tablets, sanitized, and in bottles of 500 and 1000.



NEPERA CHEMICAL COMPANY, INC.

Manufacturing Chemists



Yonkers 2, New York

facts about

Formulac



What is FORMULAC Infant Food? It is a concentrated milk containing all the vitamins and minerals a normal, growing baby is known to need. Incorporating the vitamins *into the milk itself* lessens the risk of error in supplementary administration.

FORMULAC contains vitamins of the B complex, Vitamin C in stabilized form, Vitamin D (800 U.S.P. units), copper, manganese, and easily assimilated ferric lactate. No carbohydrate has been added.

FORMULAC is in convenient liquid form, for easy preparation. The addition of carbohydrate—in the type and amount the individual child needs—creates a complete infant diet. FORMULAC is used successfully both in normal and in difficult feeding cases.

FORMULAC has been clinically tested and proved. It is promoted ethically. A product of National Dairy Research, it is available at grocery and drug stores everywhere, priced within range of even low budgets.

DISTRIBUTED BY KRAFT FOODS COMPANY

NATIONAL DAIRY PRODUCTS COMPANY, INC.
NEW YORK, N. Y.

• For further information about FORMULAC, drop a card to National Dairy Products Company, Inc., 230 Park Avenue, New York 17, N. Y.



HOW EFFECTIVE

The combined clinical value and safety of White's Sulfazole Gum has been amply confirmed by longer production than any other local chemotherapeutic or antibiotic.

HIGH topically effective salivary concentrations of sulfathiazole—averaging 70 mg. per cent—are maintained by chewing a single tablet for one hour.

HOW SAFE

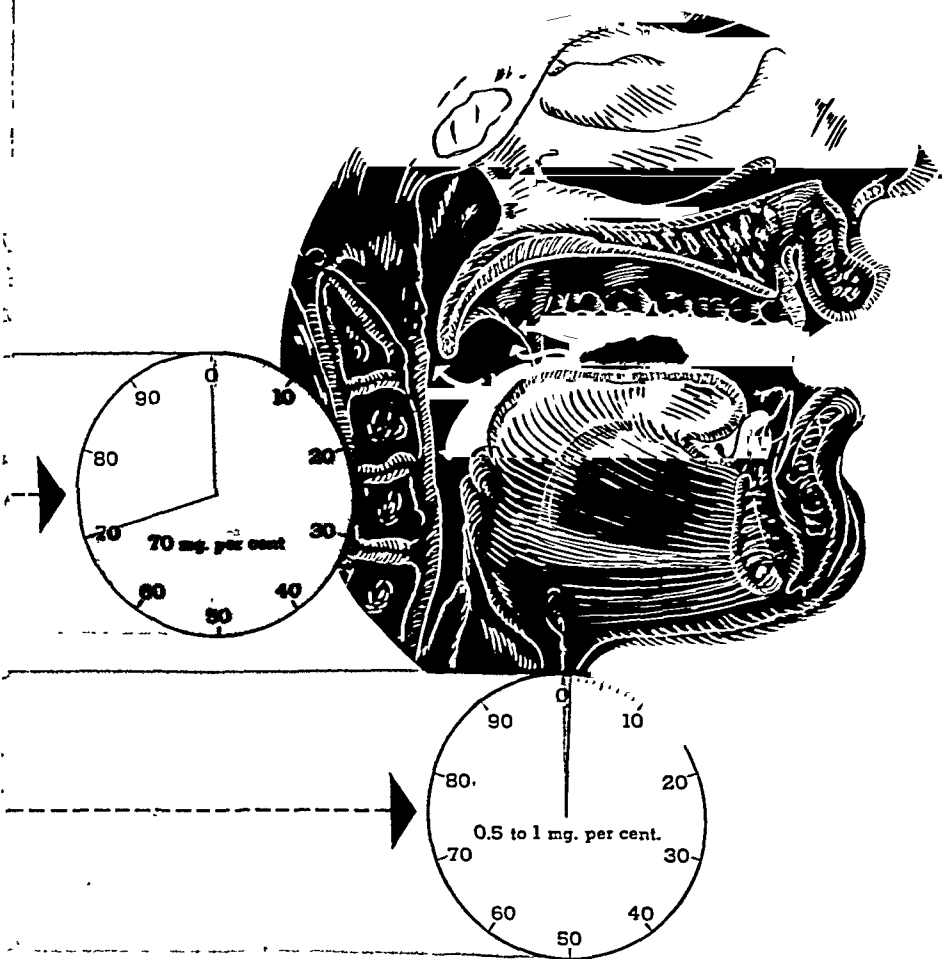
Systemic absorption is practically negligible even with maximal dosage. Blood levels are usually immeasurable—rarely approach 0.5 to 1 mg. per cent under intensive therapy—the possibility of toxic reactions is virtually ruled out.

The topical antibacterial action is persistent—the gum vehicle “reservoir” serving to release the medicament slowly at a rate roughly paralleling the drug’s solubility in saliva.

The product is stable and retains its full potency under all ordinary conditions.

Supplied in packages of 24 tablets—3¾ grs. (0.25 Gm. per tablet)—sanitaped, in slip-sleeve prescription boxes.

*A product of WHITE LABORATORIES, INC., Pharmaceutical Manufacturers, Newark 7, N. J.

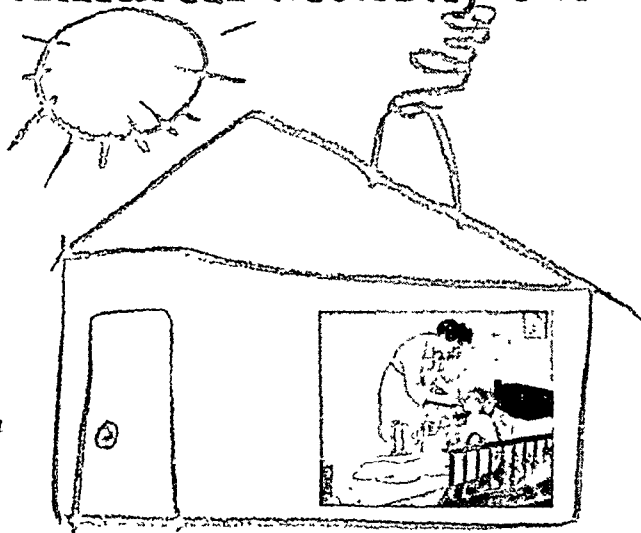


White's

Sulfathiazole gum

SAFE, TOPICAL CHEMOTHERAPY

Here's the sulfadiazine
that children actually like to take



Children
have
no
reluctance
in

taking **Eskadiazine**



Exceptionally flavorful, this fluid sulfadiazine is the ideal dosage form for your young patients. They take it willingly because it tastes good. And it relieves tired parents and busy nurses of the chore of crushing tablets and coaxing a sick child to swallow an unappealing mixture.

Important, too, is the more rapid absorption of Eskadiazine. Flippin and associates* have established that desired serum levels are attained in two hours, rather than the six hours required for sulfadiazine in tablet form.

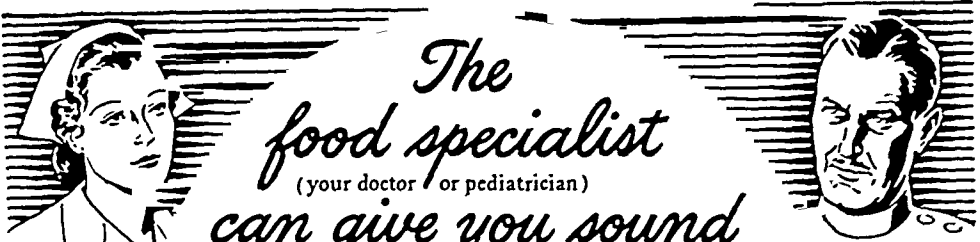
Eskadiazine

*Am. J. M. Sc. 210 141, 1915

Smith, Kline
& French
Laboratories,
Philadelphia

the outstandingly palatable fluid sulfadiazine for oral use

This is the type of advertising
Beech-Nut is running in newspapers
and magazines to reach mothers



The
food specialist
(your doctor or pediatrician)
can give you sound
advice about Infant Feeding
-and ever so many mothers are taking it

"Don't force your child to eat,"
they say, "Your baby is the best
judge of how much he needs."

But your doctor should advise you
WHAT to feed him.

And this is the time for Beech-Nut
From the beginning Beech-Nut
has cooperated closely in the selec-

tion and processing of baby foods.

They are all scientifically prepared
in spotless kitchens—the flavor
and food values are retained in
high degree.

It is not surprising that babies
like Beech-Nut foods—or that
they are good for babies.

Beech-Nut

FOODS for BABIES



"ACCEPTED"

Beech-Nut high standards of baby food
production and all Beech-Nut baby food
advertising have been accepted by the
Council on Foods and Nutrition of the
American Medical Association.

A Complete Line of Beech-Nut
Strained and Junior Foods, Meat and Vege-
table Soups, Cereals, Fruit and Desserts

Always packed in glass



Q: Is chewing a lost art?

A: *It needn't be . . . with Ry-Krisp.*

Ry-Krisp Stimulates Teeth and Gums.

Children need the crisp crunchiness of Ry-Krisp.
So do youngsters in the "teething age."

Ry-Krisp Satisfies Between-meal Hunger.

But does not spoil youngsters' regular mealtime appetites. Made of whole grain rye with only salt and water added, it is low in carbohydrates.

Ry-Krisp Is Good for Mealtime Nourishment.

Has the protein, minerals and B complex vitamins of whole rye. Delicious, tempting flavor, too.

Keep Ry-Krisp in Mind for Your Young Patients.

A SERVICE FOR YOU.

Allergy Diets — Wheat-free, Egg-free, Milk-free, Wheat-Egg-Milk-free and Restricted Diagnostic. Send for booklet containing single copies so you may order free diet pads as needed. Use coupon below.



RALSTON PURINA COMPANY, Nutrition Service
JP-E Checkerboard Square, St. Louis 2, Missouri

Please send, no cost or obligation: C2143 Allergy Diets Booklet.

Name


Street

City Zone State

CEREVim *is 19% protein*

"... cow's milk ... furnishes about 19 per cent of its calories
in the form of protein ..."

—H. C. SHERMAN¹

CEREVim  has an unusually high protein content for a cereal food, considerably more than is found in natural grains. Whole wheat, for example, contains 11 per cent. The protein in CEREVIM, moreover, is largely of animal origin (supplied by milk solids) and hence is of high biologic quality.

This extra margin of protein in CEREVIM takes on significance particularly when the child is no longer on a milk diet or rejects a well-rounded diet.

An ounce of CEREVIM provides not only about 5½ grams of protein but also the recommended daily dietary allowance of iron, thiamine, riboflavin and niacin for children up to three years of age²

¹ H. C. Sherman Chemistry of Food and Nutrition 1946

² Recommended Dietary Allowances, National Research Council 1945

Trade Mark CEREVIM Peg U S Pat Off

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY • NEW YORK 20, NEW YORK



When a Bit of *Candy*

Means So Much



From a psychogenic point of view, anything that adds to the patient's sense of well-being contributes to more rapid return of a normal outlook. Candy can serve in this capacity. When not contraindicated by the clinical situation at hand, a piece or two of candy at the end of a meal leads to a feeling of satiety in a most pleasant form. Most persons like candy, and permission to enjoy this treat during the

convalescent period especially gives encouraging assurance to the patient that the clinical progress being made is satisfactory.

That candies have a place in the dietary is evident from the many desirable foods with which most candies are made—eggs, butter, cream, milk and nuts. To the extent these foods are present, candies contribute valuable protein, B complex vitamins and important minerals. Candies also provide concentrated caloric food energy, a desirable feature when weight loss must be corrected. Thus candy enjoys a worth-while place in the dietary not only during convalescence, but also during health.

**NATIONAL
CONFECTIONERS'
ASSOCIATION**
COUNCIL ON CANDY OF THE

1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS



A BABY

SCENE I

*"a thin, pale . . .
restless, whining
infant refusing part
of its formula . . ."*



SAME BABY
Time: 2 weeks
later

SCENE II

*—now "a happy, rosy-cheeked,
smiling baby whose appetite
never seemed completely
satisfied and whose gain in
weight was remarkable."*



Between the scenes, this dramatic change was achieved with vitamin B therapy.¹ The lack of appetite from which the baby suffered is a serious matter in infancy, and one of the commonest problems in pediatrics. Many doctors now prescribe 'Ryzamin-B' No. 2 to combat infant anorexia. Its rich vitamin B content provides the needed appetite stimulation: the convenience with which it may be administered in formula or fruit juice makes it especially adaptable to pediatric needs.

Older children enjoy 'Ryzamin-B' No. 2 from the special measuring spoon, as a delicious spread when mixed with jam or peanut butter, or dissolved in milk, fruit juice or other beverages. Containing the natural B complex as a concentrate of *Oryza sativa* (American rice) polishings, 'Ryzamin-B' No. 2 also supplies potent synthetic B factors.

'RYZAMIN-B' NO. 2

BRAND RICE POLISHINGS CONCENTRATE

WITH ADDED THIAMINE HYDROCHLORIDE, RIBOFLAVIN AND NICOTINAMIDE
TUBES OF 2 OZ. AND BOTTLES OF 8 OZ.

L. Hoellner, E. F. Gurnea in *Proceedings of the Foundation of Nutrition*, N. Y., Macmillan Co., 1933, p. 273 • 'Ryzamin-B' reg. trademark



BUFROUGHS WELLCOME & CO (U.S.A.) INC., 9 & 11 EAST 41ST STREET, NEW YORK 17

February, 1948

Recent Advances In Feeding Prematures

Recent metabolic studies have established rational feeding procedures for prematures.

The initial feeding, 12 hours after birth, consists of one dram of 5 per cent dextrose. This solution is increased by one dram at 2-hour intervals if tolerated and retained.

After twenty-four hours, breast milk or formula (table below) gradually replaces the prelacteal feeding at 2-hour intervals. The volume of a feeding may be increased up to 2 drams daily until maintenance caloric requirements are fulfilled by the fifth day. If the infant shows signs of intoler-

ance, the formula increase is made slowly and the fluid requirement fulfilled parenterally.

Successful feeding mixtures consist of dilutions of powdered partially skimmed or evaporated whole cow's milk, skimmed or whole lactic acid milk. They contain high protein, moderate carbohydrate and low fat, yielding 120 calories and 1 fluid per kgm. body weight.

The problems of prematures are about the same but the solutions differ with the era. Today the moderate carbohydrate requirement is fulfilled by KARO* Syrup adequately as a generation ago. When the type of milk adapted to the infant, it may be added confidently because it is a balanced mixture of lower sugars, easily tolerated by premature infants, resistant to fermentation, non-laxative, and easily assimilated.

MEDICAL DIVISION
CORN PRODUCTS REFINING CO.
17 Battery Place, New York 4, N. Y.

R FIRST FORMULAS FOR PREMATURES

Fresh or lactic milk	6 oz.
Water	12 oz.
KARO	1 oz.
Evaporated milk	3 oz.
Water	15 oz.
KARO	1 oz.
Dried milk ($\frac{1}{2}$ skimmed)	4 tbsp.
Water	18 oz.
KARO	1 oz.

Feedings: $1\frac{1}{2}$ oz. x 12 x 2 hours

Measures: 1 oz. KARO=2 tablespoons

Caloric values: KARO, 120 per oz.; Cow's milk, 20 per oz.; Evaporated milk, 45 per oz.; Dried milk ($\frac{1}{2}$ skimmed), 35 per oz.

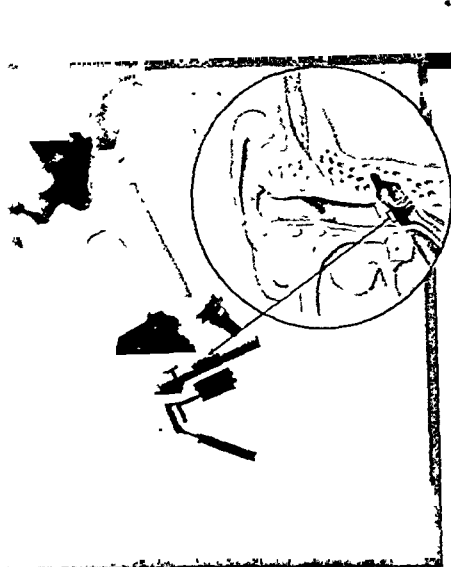
Equivalents: Red Label KARO or Blue Label KARO may be used interchangeably in all formulas.



*KARO is a registered trade-mark distinguishing this product of the Corn Products Refining Company, New York

Behind Every Bottle...A Generation of World Literature

PIONEERS in Research... and Leadership thru the years in combating



OTITIS MEDIA

DOHO in realizing the need for a potent, topical, well tolerated ear medication, yet mindful that no one formula could be suitable for all conditions... devoted every facility and scientific resource to the development and perfection of AURALGAN and OTOSMO-SAN. Each has its sphere of usefulness... each has been tested and clinically proven in many thousands of cases. *Reprints and substantiating data sent on request.*

EACH A SPECIFIC...both effective!

Auralgan

IN ACUTE OTITIS MEDIA

is a scientifically prepared, completely water-free Glycerol (DOHO) having the highest specific gravity obtainable, containing antipyrine and benzocaine... which by its potent decongestant, dehydrating and analgesic action provides effective relief of pain and inflammation.

O-TOS-MO-SAN

IN CHRONIC SUPPURATIVE
OTITIS MEDIA, FURUNCULOSIS
AND AURAL DERMATITIS

is not just a mere mixture, but a scientifically potent chemical combination of Sulfathiazole and Urea in AURALGAN Glycerol (DOHO) base... which exerts a powerful solvent action on protein matter, liquefies and dissolves exuberant granulation tissue, cleanses and deodorizes, and tends to exhilarate normal tissue healing in the effective control of chronic suppurative otitis media.

Literature and samples on request

THE DOHO CHEMICAL CORPORATION

New York 13, N. Y.

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London



**6 OUT OF EVERY 10 MEASLES CASES
WILL OCCUR IN THE NEXT 3 MONTHS!**

ARE YOU READY?

All you need by way of proof that measles are upon you is the significant 10-year graph below!

And all you really need to meet the emergency is—plenty of Immune Serum Globulin, Cutter—to make measles easier on everyone concerned. Fractionated from normal human plasma pooled from fresh venous whole blood, Immune Serum Globulin offers these particular advantages for the prevention or modification of measles:

160 mgm. gamma globulin per cc.

In measles serum, it's the concentration of gamma globulin that counts. The known and constant potency of Immune Serum Globulin, Cutter, permits low volume, adjustable dosage.

Contains no placental material

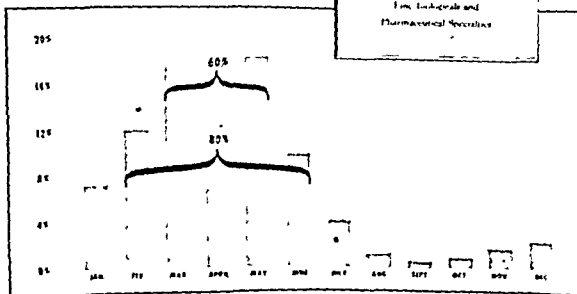
Immune Serum Globulin, Cutter, causes no side reactions, is non-pyrogenic. Easily recognizable—it is water clear; hemolysis-free.

Each 2 cc. vial of this concentrated homologous protein contains antibodies equal to 40 cc. original normal serum. Dosage is determined as follows:

For prevention—	} intramuscularly, per pound body weight
0.1 cc. Immune Serum Globulin	
For modification—	
0.02 cc. Immune Serum Globulin	

For more complete information on Immune Serum Globulin, Cutter, write Dept. 34, Berkeley 1, California.

Percent of measles cases by months from
U.S. Public Health records, total cases
1935-1945—100%



A NEW RALSTON SERVICE

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Four Forms For Four Age Groups

- birth to 3 months
- 3 to 6 months
- 6 to 10 months
- over 10 months

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the **NEW** spasmolytic and sedative
in liquid form

Robins'
DONNATAL
elixir

• Robins' "Donnatal Elixir" marks an important step forward in spasmolytic therapy. Developed for adults and children alike, this outstanding spasmolytic and sedative now greatly widens the range of its therapeutic usefulness.

• As an elixir, its exceptional palatability, its ease of administration and flexibility of dosage, together with its prompt, uniform action—all make it the spasmolytic of choice in such pediatric conditions as spastic pyloric stenosis, intestinal colic, diarrhea and enuresis.

• Donnatal's comprehensive spasmolytic effect—with an unusually wide margin of therapeutic safety—results from a synergistic combination of small, fixed amounts of the principal belladonna alkaloids, with phenobarbital. Each 5 cc (1 teaspoonful) of Donnatal Elixir equals 1 Donnatal tablet in therapeutic effectiveness.

• Donnatal is the registered trade mark of A. H. Robins Co.

Ethical Pharmaceuticals of Merit since 1878

A. H. ROBINS COMPANY • RICHMOND 19, VA.

DOSAGE Infants: ½ teaspoonful 2 or 3 times daily as necessary. Children: 1 teaspoonful 2 or 3 times daily as necessary. Adults: 1 or 2 teaspoonfuls, 3 or 4 times daily.

FORMULA Each teaspoonful (5 cc) contains
Hyoscyamine Sulfate 0.1037 mg
Atropine Sulfate 0.0194 mg
Hyoscine Hydrobromide 0.0065 mg
Phenobarbital (¼ gr) 16.2 mg.

AVAILABLE In pints and gallons

the Unique Spasmolytic
and Sedative Elixir

DONNATAL

elixir

another Robins' triumph

**Why do
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Mary need
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Growing children require vitamin D mainly to prevent rickets. They also need vitamin D, though to a lesser degree, to insure optimal development of muscles and other soft tissues containing considerable amounts of phosphorus . . .

Milk is the logical menstruum for administering vitamin D to growing children, as well as to infants, pregnant women and lactating mothers. This suggests the use of Drisdol in Propylene Glycol, which diffuses uniformly in milk, fruit juices and other fluids.

Average daily dose for infants 2 drops, for children and adults 4 to 6 drops, in milk. Available in bottles of 5, 10 and 50 cc. with special dropper delivering 250 U.S.P. units per drop.



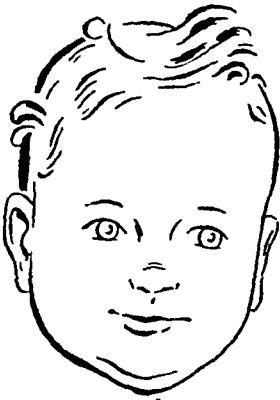
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MILK DIFFUSIBLE VITAMIN D PREPARATION
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*both respond to its
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Malt-o-Meal is an enriched farinaceous wheat cereal, flavored with bits of toasted malt. It quickly cooks to creamy consistency and easy digestibility, and imposes no undue burden on the intestinal tract. Malt-o-

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CAMPBELL CEREAL COMPANY, Minneapolis, Minn.

Malt-o-Meal



Malt-o-Meal, an enriched wheat cereal flavored with toasted malt, provides per ounce (dry weight), 0.29 mg of thiamine, 0.13 mg of riboflavin, 1.09 mg of niacin, and 2.00 mg of iron. Thus Malt-o-Meal provides appreciably more thiamine, riboflavin, and iron than does whole wheat and 78% of the niacin content of whole wheat.

Swift's Strained Meats...



"promote hemoglobin and cell formation"

Meat in the formula of 6-weeks-old infants checked drop in hemoglobin characteristic of this age

Recent clinical feedings indicate Swift's Strained Meats added to the formula of 6-weeks-old infants, not only check the drop in hemoglobin level, characteristic of this age, but actually promote hemoglobin and cell formation. In these studies, the infants' protein intake was increased 25% by the addition of approximately one ounce of Swift's Strained Meats to their formula. Infants who received this meat formula showed an average gain of 13.3% in hemoglobin content and a gain of 22.2% in red cell value of their blood. Babies in the control group, who received no meat, showed an average drop of 10.3% in hemoglobin and a gain of only 6.2% in red cell values.

Swift's Strained Meats facilitate earlier meat-feeding

The preparation of Swift's Strained Meats renders the individual particles so minute, they will pass through the nipple of a nursing bottle. These meats are easy to feed earlier in life. They provide an abundance of biologically complete proteins, B vitamins and iron.

Swift's Strained Meats are 100% meat, strained soft and smooth, trimmed to reduce fat content to a minimum and cooked to retain a maximum of the nutrients. The six varieties of Swift's Strained Meats provide flavors and textures different from baby's other foods... help him acquire the desired taste for a well-rounded diet.

For further information write

Swift & Company, Dept. S.M.B., Chicago 9, Ill.

"MEAT IN THE DIET OF YOUNG INFANTS"
Ruth M. Lester, Ph. D. and George Clark, M. D.
Journal of the American Medical Association
(J.A.M.A. 134-1215, August 9, 1947).

All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association.



Also Swift's Diced Meats for young children

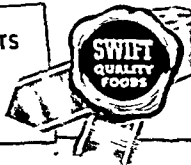
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6 STRAINED • 6 DICED MEATS

BEEF LAMB PORK
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Ready to heat and serve



SWIFT

...the most famous name in meats... first with 100% Meats for Babies

COMPLETE REMISSION

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Aural
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* DRAWS PLASMA TO SURFACE . . . * DISSOLVES NECROTIC TISSUE

* BACTERICIDAL, DEODORANT, DETERGENT, PEPTIZING, NON-TOXIC

Glycerite of Hydrogen Peroxide *ipc* Carbamide

* BIBLIOGRAPHY

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New Eng. J. Med.,
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Annals of Allergy,
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J. A. Ph., A., (Sc. Ed.)
35 304, 1946.
Literature on request.

Clinical studies concerned with the use of Glycerite of Hydrogen Peroxide in the treatment of chronic purulent otitis media demonstrated seventeen of twenty-nine patients in complete remission in 14 days and the remainder by the 38th day. The patients studied presented conditions existent for periods of 2 weeks to over 40 years. Previous treatment by the usual therapeutic means, including tyrothricin or penicillin, was ineffective in all cases.

Constituents:

Hydrogen Peroxide 1.446%, Urea (Carbamide) 2.554%, 8 Hydroxyquinoline 0.1%.
Dissolved and stabilized in substantially anhydrous glycerol . . . qs ad 30cc.

Available on prescription in one-ounce bottle with dropper.
Administration One half dropperful two to four times daily.

International PHARMACEUTICAL CORPORATION
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Meyenberg Evaporated GOAT MILK

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NATURAL MILK FOR
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FEEDING CASES



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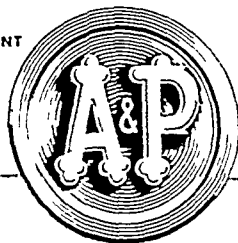
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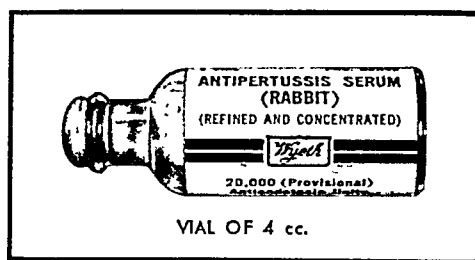
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HIGHLY CONCENTRATED...PRECISELY STANDARDIZED

Each dose...4 cc. ...contains therapeutic concentrations of antibodies and not less than 20,000 units of antiendotoxin.

Inhibits growth of *Haemophilus pertussis* and neutralizes its endotoxin...Imparts a temporary immunity to contacts, modifies and shortens the active disease . . . Tends to prevent complications.

PERTUSSIS ENDOTOXOID-VACCINE
Wyeth, for active immunization, contains 15 billion killed *H. pertussis* and 140 provisional units of pertussis endotoxin per cubic centimeter, converted to endotoxoid.
The endotoxoid component stimulates

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Vials of 6 and 24 cc.

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IN OVER **50** YEARS

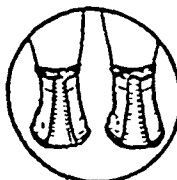
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IT PROVIDES

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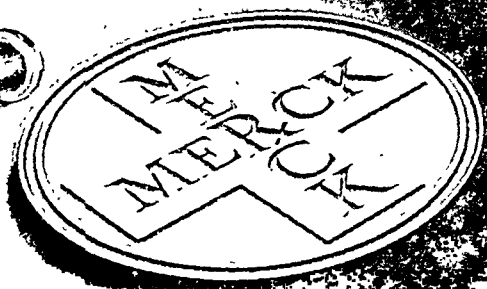
treatment of certain types of urinary tract infection, selected cases of tuberculosis, and other infections due to susceptible strains of gram-negative organisms.

Ask for the New **DATA CHART**

This new quick-reference chart gives essential data on the clinical uses, storage, preparation of solutions, administration, and dosage of Streptomycin Merck (Calcium Chloride Complex). It will be mailed to you on request. Write to Merck & Co., Inc., Rahway, N. J.

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Start him
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HOW MANY TIMES HAVE YOU WRITTEN THAT ONE . . . and wished mothers would follow your "go easy" advice? For then, babies' introduction to cereal (usually the first solid food after milk) is far easier on all concerned.

When those first teaspoonsful of cereal are *finely strained*, good-tasting Gerber's, it seems that tots get off to a happier start. They appear to favor the flavor and texture of Gerber's all through babyhood. Particularly when mothers remember . . .

Babies like the variety of a rotating schedule of Gerber's Cereal Food, Strained Oatmeal and Barley Cereal. Each is a significant secondary source of protein *and* contains *added iron, calcium and yeast*. Result? Better-than-whole-grain values for minerals and B-complex vitamins.



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our only
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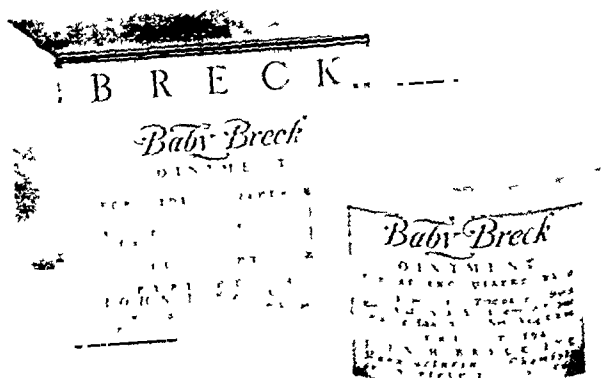
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For Aiding Diaper Rash

Sometimes keeping an infant dry is not enough to prevent a diaper rash. Baby Breck Ointment helps to protect the exposed skin through the night period. There is a minimum allergic reaction to Baby Breck Ointment due to the neutral qualities of its ingredients. One or two applications are sufficient during the day to help the milder cases of diaper rash.

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By Shan-Yah Gin, M.D., Shanghai, China.

BLOOD CHEMICAL AND IMMUNOLOGIC EFFECTS OF ADRENAL CORTICAL EXTRACT IN CHILDREN.

By Vincent C. Kelley, M.D., and John M. Adams, M.D., Minneapolis, Minn.

AN UNUSUAL ERUPTIVE FEVER INVOLVING THE SKIN AND MUCOUS MEMBRANES.

By Paul A. Bradlow, M.D., and Robert A. Schless, M.D., Philadelphia, Pa.

HEMANGIOMA OF THE LIVER CAUSING DEATH IN A NEWBORN INFANT.

By J. G. Hendrick, M.D., Memphis, Tenn.

THE STUDY OF HUNGER EDEMA IN CHILDREN.

By Eythymios P. Petrides, M.D., Athens, Greece.

HEMATOLOGIC STUDIES ON CHILDREN OF RH-NEGATIVE WOMEN COMPARED TO THOSE OF RH-POSITIVE WOMEN.

By Edith L. Potter, M.D., Ph.D., and Haskell E. Bernstein, M.D., Chicago, Ill.

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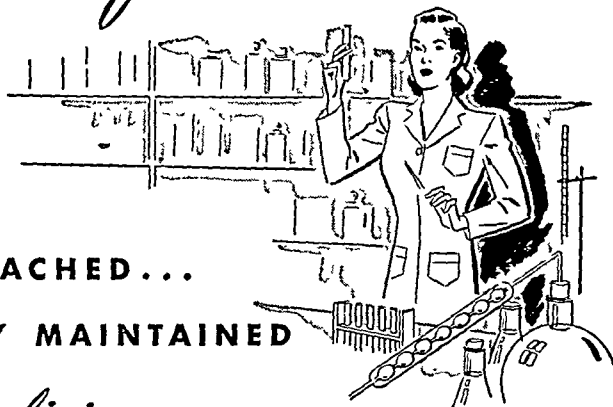
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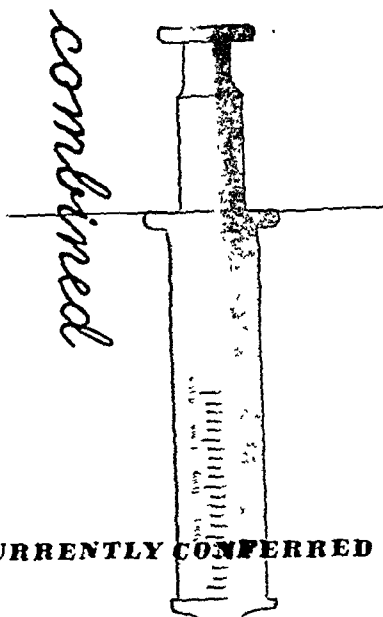
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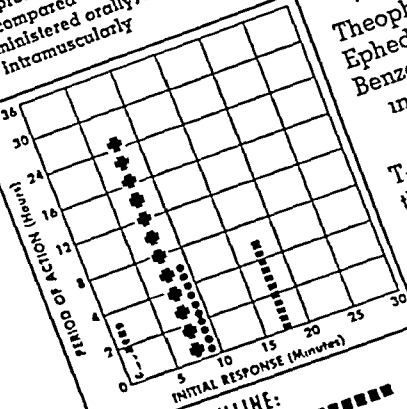
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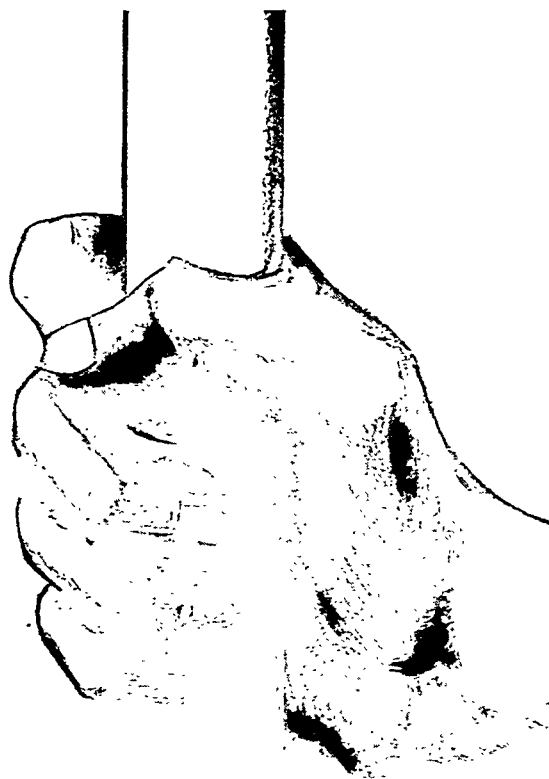
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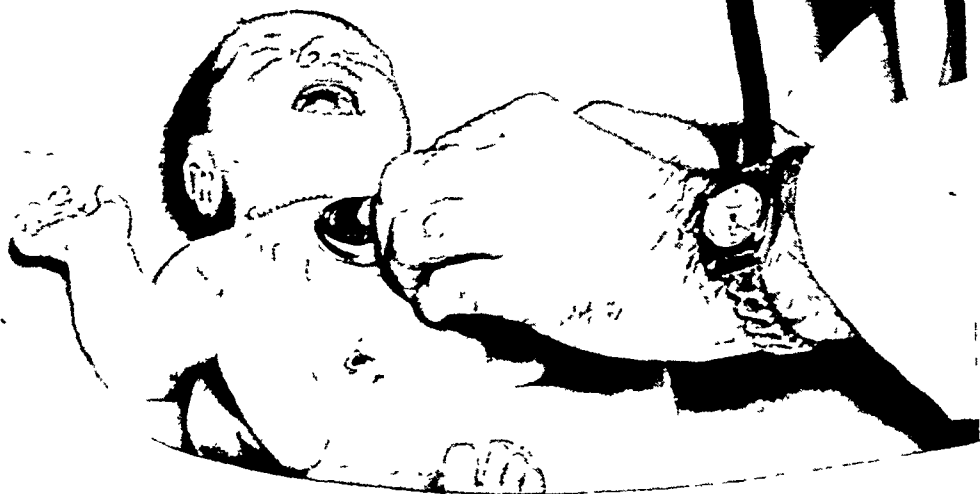
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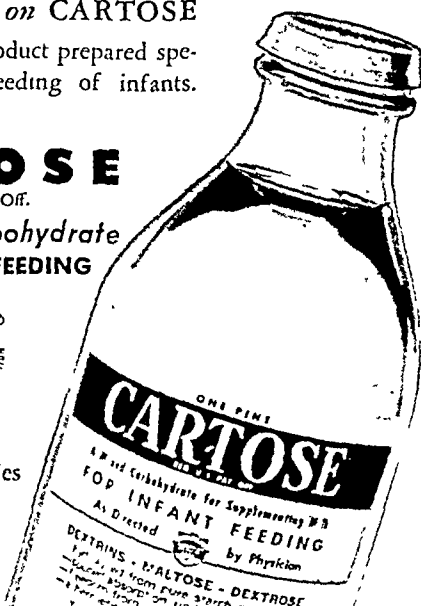
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The Journal of Pediatrics

VOL. 32

FEBRUARY, 1948

No. 2

Original Communications

A NEW TECHNIQUE FOR REPLACEMENT TRANSFUSION IN THE TREATMENT OF HEMOLYTIC DISEASE OF THE NEWBORN INFANT

DOUGLAS P. ARNOLD, M.D., AND KENNETH M. ALFORD, M.D.
BUFFALO, N. Y.

FOR years infants with icterus gravis (hemolytic disease of the newborn) have been treated by the administration of multiple transfusions. Recent investigation indicates that the blood of a baby with severe hemolytic disease is so markedly changed both qualitatively and quantitatively that an actual replacement of blood is indicated. Replacement transfusion immediately tends to rid the infant's blood of Rh antibodies, products of hemolysis,¹ and sensitized red cells^{2, 3} and replaces it with Rh-negative cells which cannot be affected by the remaining Rh antibodies.

We have seen infants with hemolytic disease who at the time of birth were so severely affected that nothing short of a replacement transfusion could have possibly saved them. In such cases it is quite probable that ordinary transfusions could be harmful either by overloading the circulation or the giving of blood which conceivably could cause intravital agglutination of the babies' sensitized cells. Witebsky and associates^{2, 4} have recently shown by slide test that in erythroblastosis fetalis the infant's red cells are sensitized and are agglutinated by otherwise compatible adult serum, but at the end of replacement transfusion this agglutination does not occur.

It is becoming increasingly clearer that replacement transfusion should be effected as early and completely as possible, especially in the severe forms of hemolytic disease. We would even suggest that if an ordinary transfusion is ever done, it should be accomplished by using Rh-negative cells, plain or in suspension.

Recently, the technique for umbilical vein replacement transfusion has been described.⁵ These cord transfusions are accomplished by using the umbilical vein at birth or within the first twelve hours of life, after which time the umbilical vein is no longer available because of thrombosis. Diamond⁶ has perfected this technique using plastic cannulae and has made this procedure practical.

Because of this early thrombosis making umbilical vein transfusion impossible after the first twelve hours, we sought other avenues for replacement

From the Department of Pediatrics, School of Medicine, University of Buffalo and the Pediatric Departments of the Buffalo Children's Hospital and the Millard Fillmore Hospital.

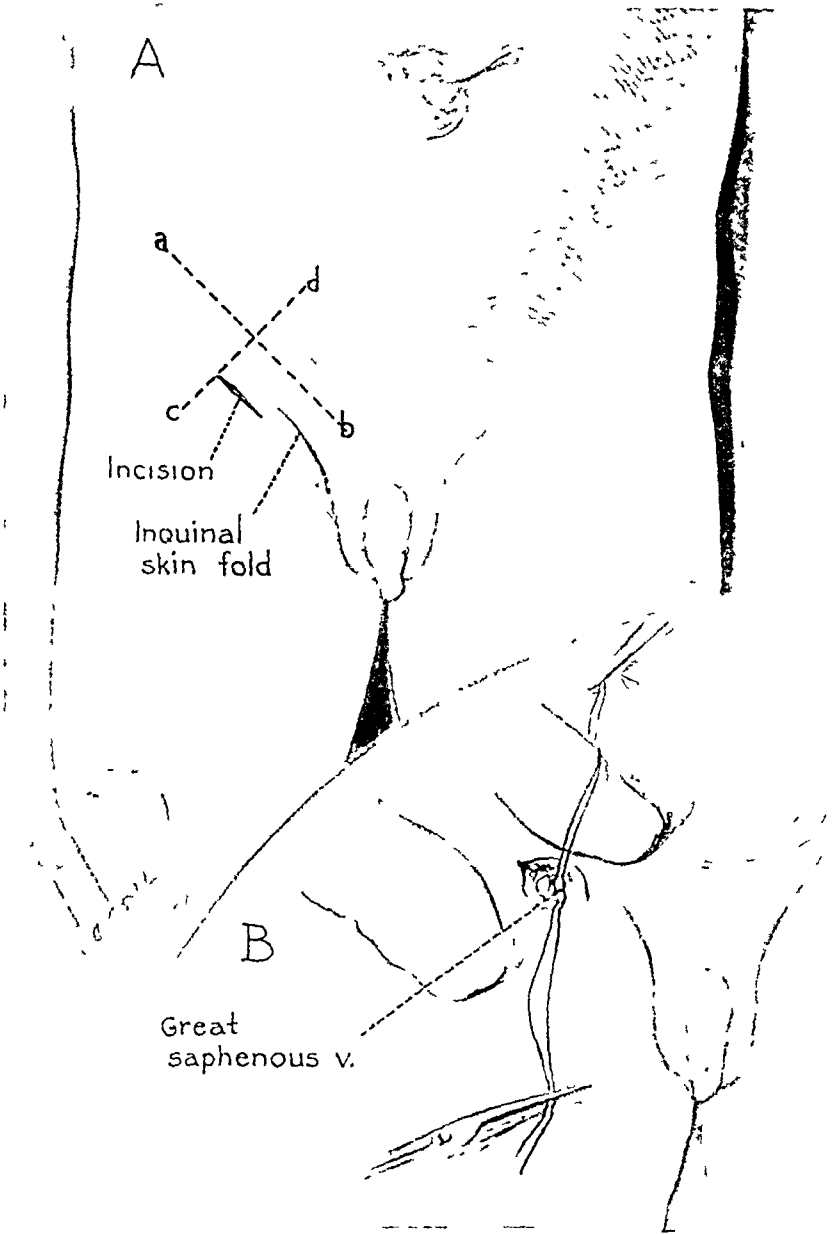


Fig 1—4, Showing incision made to expose the great saphenous vein just before it dips into the femoral vein B, The great saphenous vein exposed with double ligature around it.

of the baby's blood. Furthermore, it may not always be possible to make a decision concerning the need for replacement transfusion within the first twelve hours of life; frequently the patient is not brought to us within these first hours;

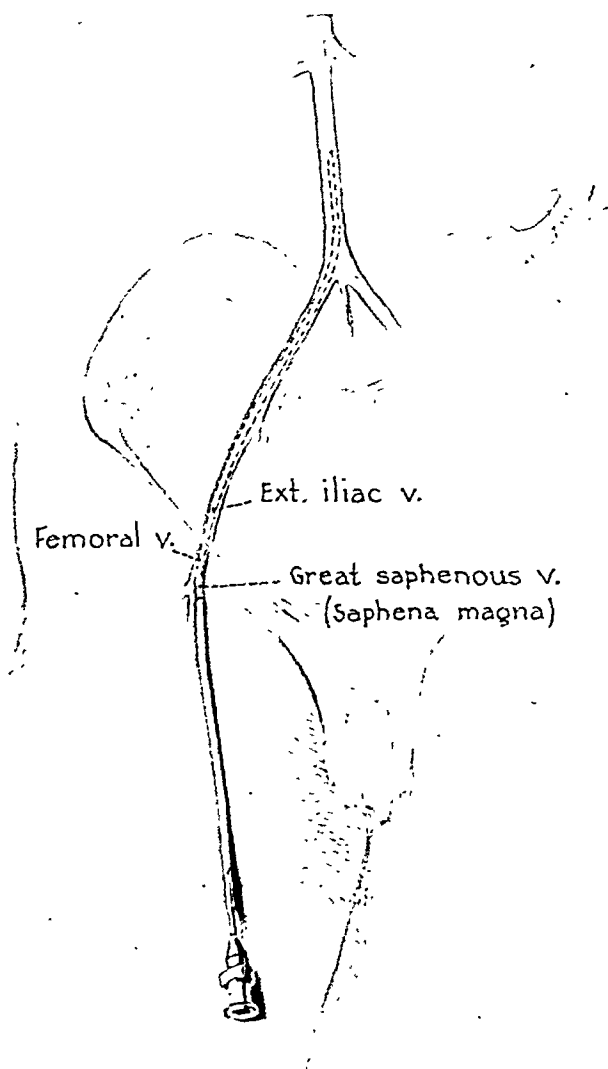


Fig. 2.—Showing direction of plastic catheter through the great saphenous vein into the femoral vein, external iliac, and up into the inferior vena cava.

in other cases the cord has been cut too short to be used. For these reasons we have developed a new method of doing replacement transfusion for the treatment of hemolytic disease of the newborn infant, saphenous vein transfusion. This type of transfusion can be done at any time and when the umbilical vein is no longer available.

There is no superficial vein in the newborn infant large enough to obtain blood rapidly and in sufficient quantity. We attempted to cannulize the saphena magna vein in the midthigh region and at times were successful. However, there are many vessels in this region, the vein is not superficial, it is not easy to identify and is often too small to cannulize.

TECHNIQUE

The proper approach to the saphena magna (great saphenous) vein in the newborn infant *must be high in the groin*. *The location of the incision is important.* (See Fig. 1.) A line is drawn between the anterior superior spine of the ileum and the pubic tubercle; (*a, b*), this is bisected (*c, d*). One to $1\frac{1}{2}$ cm. below this point, which is in the center of the upper thigh region, a one to 2 cm. transverse superficial incision is made medially and parallel to the inguinal ligament. This incision is just one-half centimeter below the skin crease (inguinal skin fold) where the thigh joins the body. After carefully spreading the skin and superficial fat with a small hemostat, a layer of superficial fascia is seen through which the saphena magna vein is visible. (See Fig. 1, *B*.) The fascia is split, the vein is carefully isolated, and a double fine catgut ligature is passed around it. Ether on a compress is then applied locally with a little pressure which prevents the retraction of the vein when cut. The vein is then incised with sharp scissors. A vein dilator is introduced for a moment; then one of Diamond's plastic catheters* 6 inches long and with a slight bevel is introduced; a rotary motion often helps engagement. The catheter is then passed into the femoral vein. (See Fig. 2.) A slight elevation of the catheter will allow the point to dip into the femoral vein more easily. The catheter is then fed 2 to 4 inches into the external iliac, the common iliac, and into the inferior vena cava. (See Fig. 3.) Almost anywhere along the line of passage a pool of blood is encountered from which a satisfactory withdrawal and replacement of blood can be accomplished. Moderate suction on the barrel of the 20 c.c. syringe will result in a steady return of blood. If too great a pressure is exerted the vein may collapse, causing cessation of blood flow. Occasionally the blood flow will temporarily stop during withdrawal; if this occurs it can be re-established by carefully readjusting the catheter, either by slightly inserting or withdrawing, until the flow is evenly resumed. When the transfusion is completed the vein is ligated. One catgut suture is sufficient to close the incision. There is no danger of subsequent edema of the leg from the ligation of this vein. This technique is simple and can be performed by anyone experienced in cannulizing the saphena magna vein at the ankle. During and after the replacement transfusion the baby should be kept warm and oxygen should be administered.

*We now use Diamond's plastic catheters, gauge 18 and 19, exclusively; the caliber used depends on the size of the vein. One of these is connected by a short needle, size 18 or 19 gauge, to a simple apparatus consisting of two three-way stopcocks, a 20 c.c. Luer-lok syringe, special tubing, and glass adaptors by means of which the withdrawal and giving of blood are easily accomplished. (Apparatus described by Louis K. Diamond.) Diamond advised that the plastic cannulae be sterilized for eighteen hours in Zephiran Alba 1:1,000 solution. The solution is then drained off and the catheters are kept dry and sterile for emergency use.

It has been shown that the alternate withdrawal and giving of 20 c.c. of blood through the same vein can, if 500 c.c. of blood is exchanged in a newborn baby, effect an 80 to 85 per cent transfer or replacement of blood.

One cubic centimeter of heparin solution containing 10 mg. or approximately 1,100 Toronto units per cubic centimeter to 150 c.c. of saline solution is used to keep the apparatus free from clots, but no heparin is introduced into the child's circulation. We believe that in this condition where spontaneous hemorrhages can occur, the giving of heparin is not without some hazard.

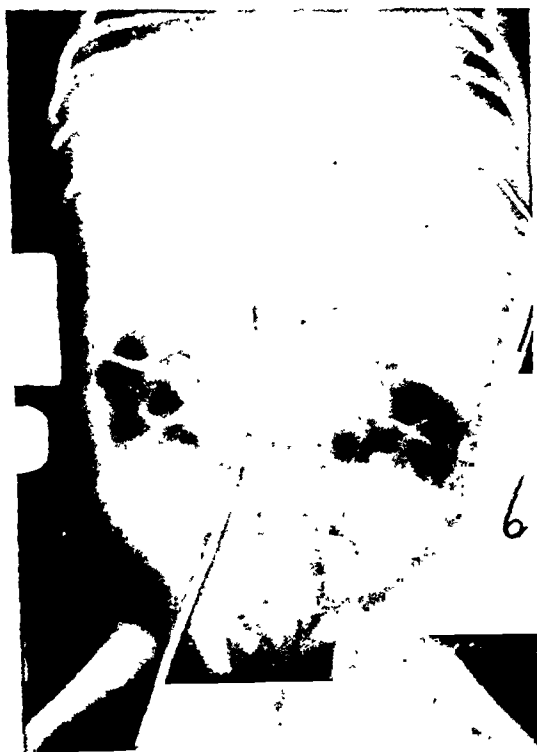


Fig. 3.—Roentgenogram of a urethral catheter passed up through the saphena magna vein into the inferior vena cava.

If the saphenous vein method is to be used, the house staff should be warned not to perform a femoral vein puncture for obtaining blood for diagnosis. Such a puncture causes extravasation of blood into the tissues, and makes the procedure of isolating the saphena magna vein more difficult.

Replacement transfusions by the saphenous vein method can be accomplished as rapidly or slowly as deemed advisable. Obviously the technical difficulty in

replacement transfusion is finding a good pool or well of blood so that withdrawal can be accomplished easily and efficiently. In replacement transfusion in the newborn we believe that at least 500 c.c. of blood should be withdrawn and replaced with 500 c.c. of Rh-negative compatible blood. In case of severe anemia, 20 to 40 c.c. of blood can be given over and above that which has been withdrawn. Replacement transfusion should not be hurried. It should take about one and one-half to two hours to complete the exchange of blood.

Because of the quantity of blood used in replacement transfusion, the blood transfused should be slightly warmed. *Care must be taken not to overheat.* It is safe to place the blood container in a water bath for fifteen minutes. The water in the bath should be at a temperature of not more than 35 to 37° C. This is to be measured by an accurate thermometer.

At the end of replacement transfusion it is customary to give calcium gluconate solution intravenously in order to combat the effect of the large amount of citrate solution used. Calcium should be given slowly and not more than 10 c.c. of a 5 per cent solution should be administered because of the possibility of heart block.

For three days following replacement transfusion we give sulfadiazine, one grain per pound per day, and penicillin, 3,000 units every three hours intramuscularly, as a prophylaxis against infection. Because of low blood prothrombin at this time of life and the hemorrhagic tendency in hemolytic disease of the newborn infant, we give hypodermically one ampule containing one milligram of vitamin K every six hours for four doses.

This method can be used in other conditions in which replacement of blood is indicated, that is, carbon monoxide poisoning, burn toxemias.

CONCLUSION

A new technique for replacement transfusion is described using the saphena magna vein. We believe this technique is of value in the treatment of hemolytic disease of the newborn infant as well as in other conditions when replacement of blood is indicated.

We are indebted to Dr. Leslie Silverstine of the Buffalo Children's Hospital staff, and Dr. Charles Stinson of the Millard Fillmore Hospital staff for their help and interest in carrying out this work. We are also indebted to Dr. Oliver P. Jones, Professor of Anatomy at the University of Buffalo, for identifying the vein used, and to Dr. Ernest Witebsky, Professor of Bacteriology and Immunology at the University of Buffalo, and Dr. Mitchell I. Rubin, Professor of Pediatrics at the University of Buffalo, for their helpful criticism in preparing this paper.

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PROPHYLAXIS OF UPPER RESPIRATORY INFECTIONS IN CHILDREN TREATED WITH ORAL PENICILLIN

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IN A previous communication,¹ 100 children, given 25,000 units of penicillin daily together with two injections of influenza virus vaccine, were reported to have experienced an average of 5.51 febrile days in twelve months, as compared with 100 controls, who had 24.3 febrile days. The conviction that influenza virus infections account for only a small percentage of the upper respiratory infections encountered in infants and young children led to the omission of inoculations of influenza virus vaccine in this present study on 148 children given oral penicillin as a prophylactic agent, and 110 control children of similar age and sex distribution.

The children reported in this study are a heterogeneous group, living in a congested metropolitan area, ranging from 8 months to 10 years of age and equally distributed as to sex and age in the treated and control groups. All have had frequent febrile upper respiratory infections, averaging four or more within the last twelve months before prophylaxis was started. Some of these had acute follicular tonsillitis, others had pharyngitis, many had acute cervical adenitis, a number had recurrent otitis media, and others had frequent attacks of bronchitis. The term "upper respiratory infection" has been used because of the virtual impossibility of segregating grippe, influenza, sore throat, pharyngitis, tonsillitis, and cervical adenitis from each other in children, since these are terms which "merely direct attention to an evident localization and lose sight of the fact that we are really dealing with an underlying disease of more far-reaching potentiality."²

PROPHYLAXIS

The 110 control children were given no medication. The 148 children selected for prophylaxis, seventy-nine boys and sixty-nine girls, were given 50,000 units of penicillin twice a day for the twelve months of observation, wherever possible from one-half to one hour before a meal. The oral penicillin-buffered tablets were used, no particular manufacturer being specified. Every effort was made to keep the prophylactic and control groups of similar constitution, in respect to age, sex, and susceptibility to upper respiratory infection.

No penicillin blood levels were attempted in this study, inasmuch as figures in the literature are ample for this purpose. Mothers were instructed to keep records of temperatures in the children if there was any suspicion of illness. Since this study was made in an off-measles year and infant morbidity from other causes was very low, practically all the febrile infections were upper respiratory in origin. All febrile cases were seen by one observer, and the records of daily temperatures in each febrile episode were adequately kept.

Reactions.—One child had an urticaria which forced discontinuance of the drug; another a glossitis which vanished when the practice of chewing the

TABLE I. TABLE OF AGE AND SEX DISTRIBUTION

NO. CASES	AGE (YR.)						SEX	
	UNDER 1	1-2	2-3	3-4	4-5	5-10	MALE	FEMALE
148 treated	8	50	48	15	12	15	79	69
110 controls	7	39	34	8	10	12	57	53

TABLE II. RESULTS

NO. CASES	UPPER RESPIRATORY INFECTIONS			
	12 MO. PRECEDING		12 MO. AFTER	
	AVERAGE ATTACKS	FEBRILE DAYS	AVERAGE ATTACKS	FEBRILE DAYS
110 controls	4.52	14.24	3.81*	14.04*
148 given prophylaxis	5.05	16.76	2.3	4.24

*No prophylaxis with penicillin.

tablets was interdicted; and a third, a syndrome resembling a flareup of a previous epidermophytosis. On the whole, the prophylactic procedure was remarkably free of reactions.

DISCUSSION

At this point, some discussion of other procedures in the prevention of upper respiratory infections in infancy and childhood seems in order. The value of tonsillectomy and adenoidectomy in selected groups cannot be questioned. Kaiser's³ conclusions that the incidence of follicular tonsillitis and cervical adenitis is sharply reduced, but of bronchitis somewhat increased, are still accepted. Of the 110 controls, 46 (41.8 per cent) had had a tonsillectomy and adenoidectomy, and of the 148 treated children, 55 (37.2 per cent). Tonsillectomy and adenoidectomy were not resorted to in larger numbers because 106 of the 148 (71.6 per cent) were under 3 years of age, and experience has shown a larger number of recurrences, especially of adenoid growth, with operation under 4-5 years of age. In many of these children, an attack of acute follicular tonsillitis seemed to subside in three or four days, but examination showed enlarged cervical glands, and febrile periods occurred at irregular intervals for weeks. This seems explainable by the concept of streptococcosis discussed by Powers.⁴ Perhaps, if every streptococcus infection were treated adequately over a long period of time (a week or more) such recurrent infections would be obviated. We are too prone to stop treatment after one or two days of "no fever." In the tonsillectomized children, a very common finding was lymphoid granules in the tonsillar bed and all over the post-pharyngeal area, accompanied by some postnasal drip. Crowe's⁵ work on the beneficial effects of radiation in such cases is well known but hard to apply in such a young age group.

Sulfonamide prophylaxis of upper respiratory infections is well established in spite of Siegel's⁶ almost negative results and Damrosch's⁷ warning against the production of sulfa-resistant organisms of a highly invasive character. The necessity for constant blood and urine checking to avoid agranulocytosis, hemolytic anemia, and hematuria, have limited the use of sulfonamide in prophylaxis.

The questions to be answered in the use of oral penicillin in such a program of prophylaxis are: (a) Are such small doses effective? (b) Are allergic reactions frequent? (c) Would such a program of small doses favor the development of penicillin-resistant pathogens?

First, the question of the dosage brings to the fore the sharp contrast between American and British thought on the subject. Practically all of the American work has been done on adults.⁸ A blood level of 0.03 to 0.04 units per cubic centimeter or higher is usually attained, with oral doses approximately five times as much as those given by the intramuscular route. When given on an empty stomach, considerably greater blood levels are attained than after a meal. Schnitzer⁹ working with experimental pneumococcus pneumonia in mice, and Wilson and associates,¹⁰ working on rats, found that ten times as much oral penicillin is needed as parenteral. English observers¹¹ seem impressed by the low total and free gastric acidity in children up to 3 years of age, and by the imperfect renal function in infancy, and present evidence that oral administration of 5,000 units per pound body weight in twenty-four hours gave blood levels of 0.1 to 1.2 units one-half to six hours afterwards. All agree that these blood levels produced complete bacterial inhibition in practically all the patients tested, and that the serum penicillin levels from oral administration were at least as good as those from intramuscular administration, and, in fact, in many instances inhibitory levels were maintained much longer. It seems very likely, then, that the children in this study who received 50,000 units twice a day one-half to one hour before meals had satisfactory penicillin levels. This dosage may not establish a therapeutic level around the clock (twenty-four hours). However, since figures of 0.02 to 0.03 are common minimal effective levels for inhibition of standard strains of *Staphylococcus aureus* and *Streptococcus hemolyticus*, it seems probable that at least inhibitory levels exist in these children after twice-daily administration of 50,000 units. A sharp distinction must be made between inhibitory and therapeutic blood levels of penicillin. It was not the purpose of this work to attain a level which would cure frank disease; in other words, the objective was prophylactic and not therapeutic. The question is whether a low level of penicillin in the blood would be inhibitory to the vast majority of pathogenic organisms which may find entrance to the nose and throat of well children. Theoretical considerations would suggest that in vivo levels need be less than those found in vitro, inasmuch as the immune defenses of the body also come into action. A recent study by Eagle¹² is interesting in this connection; in the case of the C-203 strain of *Streptococcus pyogenes*, a concentration of penicillin of 0.006 μg had a definite, if slow, bactericidal action, while a maximal rate of killing was attained at 0.064 μg per cubic centimeter. Here the spread between what might be called inhibitory and therapeutic concentrations is almost tenfold. More quantitative work is needed on this point: from a clinical viewpoint, the results of this paper show a very definite inhibitory effect of oral penicillin administered as mentioned.

The second question is that of injurious effects. Dermatitis,¹³ an allergic response,¹⁴ delayed serum sickness,¹⁵ hypersensitivity simulating serum sickness,¹⁶ and hydrarthrosis and an anaphylactic shocklike syndrome¹⁷ have been reported

(Morginson¹⁸ has reviewed the literature). These have been practically always after intramuscular administration or topical application. In this series, one child had urticaria, another glossitis, and a third an epidermophytosis.

The last argument against penicillin prophylaxis, that the continuance of small doses would favor the development of penicillin-resistant organisms, requires careful consideration. Demeree¹⁹ showed that in vitro development of penicillin resistance does not result from the action of penicillin on the organisms but originates through a selective process whereby nonresistant organisms are eliminated by the drug, and, through mutation, the more resistant cocci multiply. Rake's²⁰ work indicated that an acquired in vitro resistance to penicillin may not be of great consequence therapeutically, due to a loss of virulence by organisms which undergo this change. "This is in direct contrast to bacteria which develop sulfonamid fastness; the virulence of such organisms remains unimpaired." Spink²¹ showed that there was a fundamental difference between penicillin resistance acquired in vitro and in vivo. "Since penicillin resistance developed in vitro seems to be temporary and associated with a loss of virulence of the organism, it is probably of little clinical significance. The in vivo type of penicillin resistance, which appears to be a permanent characteristic and is accompanied by the production of penicillinase by these strains, is of considerable importance clinically. If inadequate concentrations of penicillin are present, the more susceptible bacterial cells may be eradicated, leaving an opportunity for the resistant variants to multiply." This directly contradicts an English worker.²² There is no agreement on this point as yet. Our hospitals have not been receiving large numbers of patients with penicillin-insensitive organisms, although undertreatment at home is a very common occurrence. In my previous series¹ and in the present series, there were 248 patient years of prophylaxis. If the production of in vivo penicillin resistance by small prophylactic doses were a common clinical occurrence, surely some evidence should have been available. On the contrary, those children who did develop upper respiratory infections in spite of prophylaxis invariably responded to the usual therapeutic doses within two or three days.

• Since the completion of the study, a report²³ has appeared in which 50,000 units of oral penicillin were given twice daily for twelve months to seventy rheumatic children, ranging in age from 6 to 14 years.

- (a) 50,000 units one hour before breakfast, 0.20 units per milliliter serum (av. 500)—30 to 60 minutes later:

Maximum, 0.29	30 minutes
Maximum, 0.25	60 minutes
Maximum, 0.04	120 minutes
not detectable beyond 2 hours.	

A significant decrease in blood concentration occurred with increase in body weight:

Less than 75 lb.—0.24
75 to 100 lb.—0.22
100 lb. or more—0.16.

- (b) 50,000 units just before breakfast—0.15 average level, somewhat lower on the whole.
 (c) 50,000 units just after breakfast—negligible levels.
 (d) 50,000 units just before supper—0.12 average level.

These results are consistent with the penicillin levels for children of different ages and weights predicted from the English literature. In recapitulation, therefore, it seems probable that the 148 children in this study who received 50,000 units of oral penicillin as a buffered tablet one-half to one hour before breakfast and supper attained satisfactory levels.

If these figures are compared with Eagle's¹² figures of definite bactericidal action with 0.006 units and maximal rate of killing at a level of 0.064 units, it seems probable that the plasma levels of these children contain a substantially bactericidal level of penicillin for a large portion of the twenty-four hours.

SUMMARY

1. One hundred and forty-eight children from 8 months to 10 years of age have been given 50,000 units of oral penicillin as buffered tablets one-half to one hour before breakfast and supper for twelve months, with a control group of 110 children receiving no medication.

2. The control group experienced no reduction in the average number of upper respiratory infections or the average number of febrile days in the twelve months of observation, as compared with the previous twelve months.

3. The group given penicillin prophylaxis experienced a reduction in the average number of upper respiratory infections from 5.05 in the previous year of no penicillin prophylaxis to 2.3 in the year of penicillin prophylaxis (45.5 per cent) and the group experienced a reduction in the number of febrile days from 16.76 days in the previous year to 4.24 days in the year of penicillin prophylaxis (25.3 per cent).

4. No penicillin levels are reported for this study but English and late American sources are quoted to show that such dosage would, in children of these ages and weights, produce levels definitely bactericidal.

5. The literature is reviewed to show the very controversial nature of the widely held belief that this prophylactic procedure would do harm by the production in vivo of penicillin-insensitive organisms; no such cases occurred in the 148 now reported and the 100 previously reported.

6. The suggestion is made that if these results can be corroborated in larger series over a longer period of time, a relatively inexpensive and harmless prophylaxis of upper respiratory infections in young infants and children will be possible.

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ADDENDUM

In a recent article, G. S. Husson (*J. PEDIAT.* 31: 651, 1947) found that 20,000 units gave good levels for four hours in infants to 5 months of age.

A SUBSTITUTE FOR SKELETAL AGE (TODD) FOR CLINICAL USE: THE RED GRAPH METHOD

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THE Red Graph method is a technique for identifying stages of bone development and reducing them to graphic expressions. The method was named from a new form of illustrative graph which was introduced in 1946 with the revision¹ of Todd's *Atlas of Skeletal Maturation*.² This revision includes a new standard of reference from which bone ages may be assessed from roentgenograms according to the Todd inspectional method^{2, 3} described in the original edition. The outstanding difference between the original Todd standard and the revision is that the revision is designed to permit from each roentgenogram of the child an analysis of the developmental symmetry of the several bones of a functional unit of the skeleton as well as the skeletal age (Todd). A new form of graph which reduces the expression of developmental symmetry to a graphic expression is discussed and illustrated in this revision. The authors believe that the Todd inspectional method of assessing bone development from roentgenograms is fundamental, and that the new form of graph is useful to the clinician. This paper describes how the new graph differs from the Todd graph in form and meaning.

HISTORICAL BACKGROUND OF SKELETAL AGE (TODD)

In 1937 Dr. T. Wingate Todd presented his standard of reference and described his roentgenologic technique for assessing the stages of skeletal development which the child has reached.² This assessment of developmental progress in bone is made by timing the changes through which the articular surfaces of the bone and the epiphyseal cartilage plate progress during childhood to form the joints of the body. Todd's method of assessing the skeletal age of each bone had been discussed in 1936 by Dr. Charles D. Flory, who actually presented the first standard for the inspectional method, and it had also been touched upon as early as 1928 by Dr. Milo Hellman.⁴ Both Hellman and Flory have stated that they consulted with Todd prior to publishing their own material on skeletal changes, and the technique is, therefore, commonly known as the Todd inspectional method.

The 1947 revision of the Todd standards of reference, published² and unpublished, began in 1941. During the war a number of different people contributed ideas on practical clinical applications of the Todd inspectional method.

Northwestern University Studies in Nutrition at the Hillman Hospital Birmingham, Alabama, from the Department of Nutrition and Metabolism, Northwestern University, and from the Research Laboratories of the Children's Fund of Michigan.
The studies at the Nutrition Clinic, Birmingham, Ala., were supported by grants from the American Dry Milk Institute, Inc.

Eight test copies of the new standards were issued to clinics in the United States and abroad during the paper shortage. One of the ideas contributed was the technique for expressing the symmetry of skeletal maturation graphically which is described in this paper. The first illustrative graph used experimentally in the clinic was drawn in red color, and it was called the Red Graph to distinguish it from the Todd graph. The new standard and this graph became associated. The distinguishing name for the revision was chosen, therefore, according to the new graph, and is now known as the Red Graph method of assessing developmental symmetry in regions of the skeleton divided according to function.

The Todd inspectional method of assessing skeletal development is based on bone form. Todd taught that this is the logical basis because growth of bone is a series of histologic changes in cell complexity whereby bone salts are modeled into a hard cortex. Usually these changes in cell complexity and the modelling are accompanied by general increase in bone size although there is not an equal size increase in all parts of a bone. Bone, of course, is so constituted that it cannot *decrease* in size during growth, and while this physical property makes bone unique as a body tissue, there are maturational changes within growing bone that are not reflected by its size.

Skeletal age (Todd), therefore, is based upon the modelling of the bone cortex during growth, particularly in the region of joints. The Todd graph and the Red Graph are derived from the ages when the successive intermediate features of the adult bone cortex appear. There are a number of successive features of each joint surface which are universal. Since these features of the joint appear "stepwise" to replace each other, these intermediate steps¹⁻⁴ have become known as skeletal maturity indicators. The standard of reference both for the Todd graph and for the Red Graph, then, consists of a series of roentgenograms which illustrate those successive skeletal maturity indicators which are universal and which, therefore, one may expect to find in every child before his bone attains its adult size and form. Their value in the clinic rests upon the fact that the speed at which these indicators replace each other is a measure of the child's bone growth.

SIGNIFICANT DIFFERENCES IN THE FORM OF THE TWO GRAPHS

A difference of greatest importance between the Red Graph and the Todd graph is that one is a zone and the other is a curve (see Figs. 1 and 2). This difference in form is due to the fact that for the Red Graph the age equivalents of both the *most advanced* and the *least advanced* bone in a child's roentgenogram are plotted on the graph paper to construct the zone. For the Todd graph the bone age equivalents are first assessed from the same roentgenogram as the Red Graph, but they are then *averaged*, and any average obviously appears on the graph paper as one point. It is apparent to the reader at once that after plotting the maximum and the minimum assessment, the examiner has an expression of developmental *symmetry* of the skeletal region in the Red Graph. But after he has reduced the age equivalents of the several bones to the average used for the Todd graph, he can only compare the skeletal age (Todd) of the whole region with the child's chronological age as a measure of developmental

symmetry, until successive roentgenograms are made. Then the observer will not be studying the same conception of symmetry of skeletal development, as will be discussed further in this paper.

DIFFERENCES IN THE MEANING OF THE TWO GRAPHS

The Red Graph stemmed from the same observations as the Todd graph up to the point where the average of the equivalent bone ages is calculated. The locations on the graph paper of the upper and the lower edges of the Red Graph zone (Figs. 1 and 2) are determined by the progress which two representative bones in each of the functional regions of the skeleton have made toward the adult form. The reader immediately asks two important questions: (1) How valid is it to use two bones (i.e., skeletal maturity indicators) as representative of a functional unit of the skeleton? (2) Why is the Todd graph, which is derived from a representative sampling of several bones in that part, questioned? When some thought is given to the following biological principles, an answer is given to these two vital questions simultaneously:

1. The structural and functional maturity of a child's body is not revealed clearly by the *average* of the maturities of the functional parts of his body, for such an average discounts the development of the most advanced organs or parts and at the same time "adds to" the maturity of the lagging organ or part. The locale of the tissue strength or weakness is thereby obscured and the summarizing curve becomes a nonspecific indicator of symmetry.
2. The process of cartilage replacement by bone is not an interstitial process although it is an absorption-addition process. No bone is "filled into" a growing cortex already ossified.
3. There is a *universal order* in the steps whereby each joint surface is shaped. This order and its universality are not altered by the nutrients furnished to the child's bone, nor by his health and natural speed of bone growth. No known factor alters the order of the steps whereby a given joint surface completes its adult form. If growth at the cartilage plates is disturbed,⁵ the joint surface modelling pauses until the condition is changed. If the interrupting factors affect growth of the bone radically, at length a caricature of the joint and the shaft is formed and it becomes a permanent part of the living tissue of the body. Ricketic bone is an example. The size, relative curvature, density, and composition of a joint surface are never the same in any two children, but no one mistakes a child's tibia for his femur.

The physiologic accuracy of using only the most advanced and the least advanced bone age equivalents of a functional part each time as the determinator of the edges of the Red Graph zone needs much further study. The writers regard them as comprehensive expressions of skeletal symmetry in the part as a rule, *since the assigned age of every bone falls between the upper edge and the lower edge of the zone*. Skeletal symmetry is important because the least advanced bone must be brought through the full course of its maturation cycle,

and this should proceed on time as nearly as possible. In cases of nutritive failure and lagging growth, one is concerned about the retarded parts and the "runaway" parts alike for they are often entrenched for many months in the body's effort to recover equilibrium. Other bones are likely to be stabilized somewhat too if the least advanced bone can be accelerated at all.

The most advanced bone serves interestingly as something of an indicator of the child's potential when a decision has to be made about what the optimum developmental speed for his bone should be. Todd pointed this out when he said:

"This brings us to the chief principle in the assessment of maturity, a principle which otherwise is difficult to comprehend. Since skeletal age is not a goal in itself but is employed as an indicator of bodily maturity, it is evident that the centers in which ossification progress is impaired will be fallacious criteria of maturity [i.e., the optimum bone development at which to aim]. The principle of assessment is therefore the utilization of the most advanced centers, not the average of all as a guide to actual bodily maturity. . ."²

If one decided that it is desirable to bring all of the child's bones to the level of the most advanced bone, he must, of course, be sure that this one maturity indicator is not by chance greatly exceeding a speed of growth which is desirable for the child in question. For calculating the desired skeletal development level toward which the child should be guided, then, these departures from the Todd inspectional method are proposed:

1. First plot the equivalent ages of the most advanced and the least advanced bone.
2. Draw the oblique straight line which indicates that according to this standard of reference all of the child's joint changes are expected to proceed at the rate of one skeletal month increase per month of increase in his age until epiphyseal diaphyseal fusion occurs.
3. Then enter the child's skeletal age (Todd) as a *limited* indicator of developmental status of the part, with due regard for the fact that it is an average and that the maximum and the minimum bone ages used for the Red Graph are *not deviations from this average*.

INTERPRETATION OF A RED GRAPH

The Red Graph has a minimum of two parts and an optional third part. The following interpretation of the parts of the graph is offered by the authors:

Part I. The Upper Edge.—This edge is plotted according to the ages assigned to the most advanced bone seen each time when the skeletal region is x rayed. The upper edge, then, denotes the most nearly complete replacement of cartilage by bone which the child has attained at the age considered. (The child's bone *potential* is always unknown.)

Part II. The Lower Edge.—The lower edge has been plotted from the ages of the least advanced bone seen each time the same skeletal part of the child has been x rayed. It denotes the smallest amount of progress toward cartilage replacement by bone which the child has attained either in the selected part or in the entire skeleton as the case may be, at the age considered. The bone potential remains unknown, but it is desirable that this less mature bone be expected to develop at nearly the same speed as the bone which determines the location of the upper edge of the graph.

Part III. The Zone.—The area between the upper and the lower bone age equivalents is shaded in to indicate that the maximum and the minimum bone ages are to be considered simultaneously. In the light of what is known at present about the uniformity of the composition of bone in a functional part, it seems unnecessary to plot every bone age assessment between the maximum and the minimum although this information is valuable.

INTERPRETATION OF FIGS. 1 AND 2

FIG. 1

Fig. 1 is the Red Graph and skeletal age (Todd) of the hand of a child who was under treatment for lipemia. He is child R. B., whose history has been discussed in page 1,395 of Macy's Monograph, *Nutrition and Chemical Growth in Childhood. II. Original Data.*⁶ This case was chosen by the authors as an example of what can be learned from a single roentgenogram.

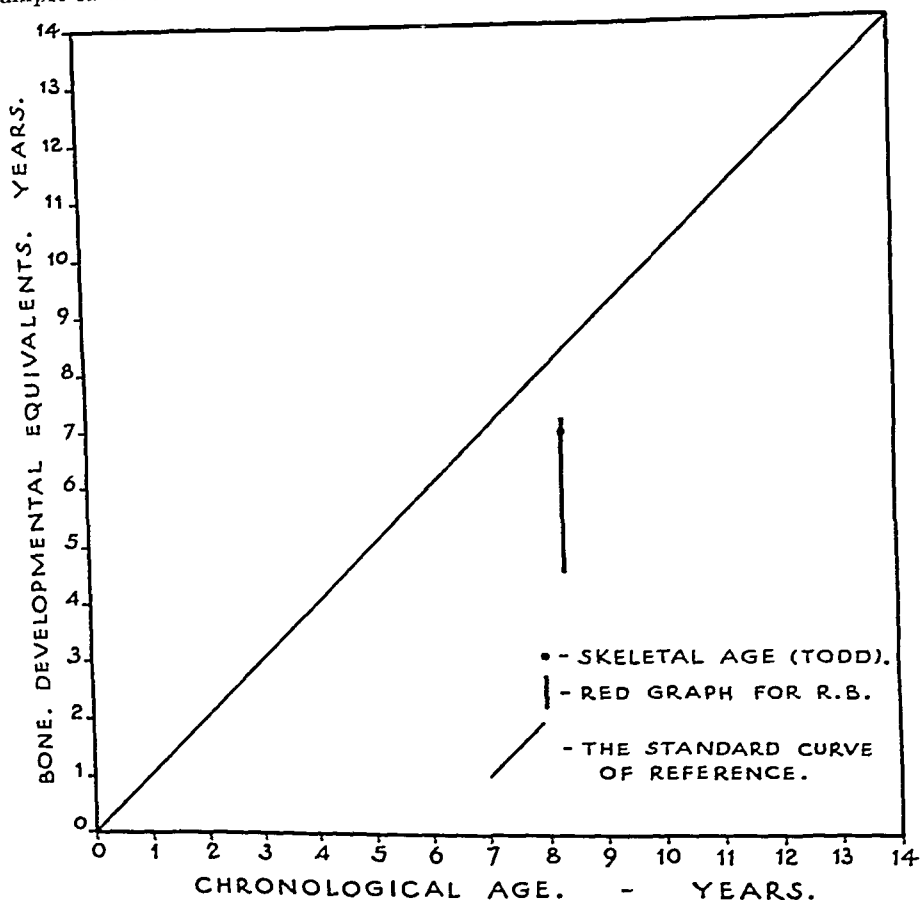


Fig. 1.

The Upper Point.—The boy's capitate was his most mature bone according to this standard of reference.¹ It was assigned the developmental equivalence of 86 months. Since the child was 101 months old, he was on a slow schedule of development according to this edge of his Red Graph.

The Lower Point.—The lunate was the least mature bone in the hand according to this standard of reference.¹ It has been assigned the developmental equivalence of 54 months. Even if the slow schedule suggested by the upper edge of the Red Graph is the most favorable speed for him, the difference

between 54 months and 86 months indicates that the child has a significant amount of asymmetrical development in the skeletal part, and suggests the need for studying carefully the status of other body parts which influence bone growth before proceeding with the growth summary for the clinical history.

The Zone.—Dr. T. Wingate Todd had personally assigned this hand a skeletal age of 84 months according to his original standard of reference. Thus by inference one can see without plotting in the age equivalents for every bone that the lower edge of the graph (an equivalence of 54 months) indicates significant retardation, for Todd's value is the average derived according to a standard of reference which resembles the Red Graph standard of reference closely.

Discussion of R. B.—It seems logical to the authors to consider first the events in the child's life near the time when the child was about 4 years old rather than to focus attention on the fifteen months of retardation suggested by the difference between the child's age and the upper edge of the Red Graph. This is indicated because cartilage replacement by bone is expected to begin in the lunate near $3\frac{1}{2}$ years of age according to the Red Graph standard of reference.¹ At 101 months this child appears to be on a slow asymmetrical schedule of cartilage replacement, and the initial preparation for cartilage replacement by bone when he was $3\frac{1}{2}$ years old could have been proceeding slowly, too, at that time.

Skeletal asymmetry could be due to skeletal anomaly, but none was evident in the region of the lunate or elsewhere in the hand at 101 months.

Whatever the cause of the developmental asymmetry in his bone may be, it seems clear that the child has been carrying a physical load for many months which reached into his bone. Whether the cause is constitutional failure which prevented the absorption of the proper amount of nutrients or lack of proper food is not indicated, of course, by the boy's Red Graph. This amount of retardation at this age does suggest a constitutional basis, for by 8 years of age children's bones have recovered from the effects of the brief severe illnesses common to early childhood, and this amount of skeletal asymmetry and retardation seldom persists by 9 years of age.

FIG. 2

Jean and Garnie are two children from the same family who have been studied in the Nutrition Clinic of the Hillman Hospital of Birmingham, Ala. Garnie is a boy and Jean is his older sister. In order to conserve space, neither their roentgenograms nor their complete case histories are included. Garnie was examined fifty-six times in six years and Jean fifty-four times, in addition to the daily observations which the social service workers made of these children during the twenty months a milk supplement was given.* The family has been in a state of nutritive failure ever since these children were first examined in the clinic in 1940. The following is a brief extract from the detailed summary

*These two children were given 3 oz. of defatted dry milk solids each day except on Sundays for a period of fourteen months in the case of Jean and twenty months in the case of Garnie. The milk was furnished through the courtesy of the American Dry Milk Institute, Inc. It was suspended in water, iced overnight and fed to the children by one of the social workers on the staff of the Nutrition Clinic.

of the physical condition of the family of these two children made by Mrs. Nelwyn Dill, one of the staff members of the Nutrition Clinic:

Family History, in 1947.—The family consists of eleven children, ranging in age from 22 years to 9 months. The mother and father are 43 and 44 years old, respectively.

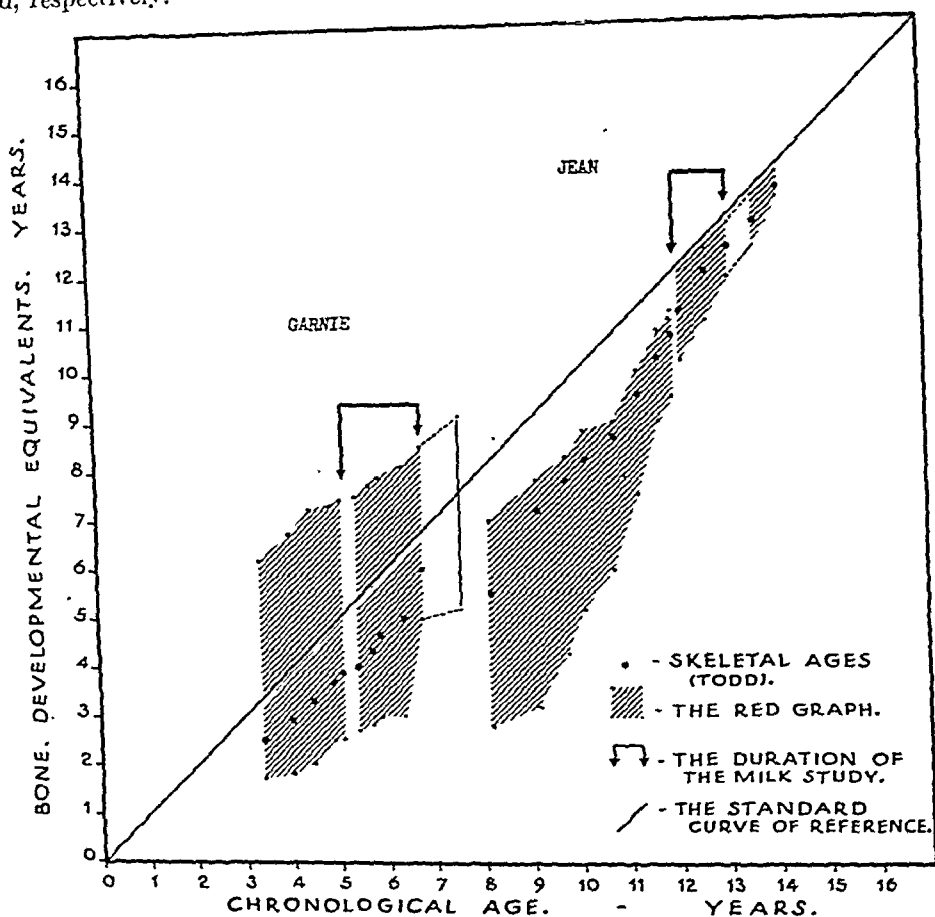


Fig. 2.

Every member of this family except the two youngest girls and the youngest boy has been under observation or treatment by the Nutrition Clinic staff since 1940. The father, all his life, has had symptoms of subclinical pellagra. In 1940 he suffered with burning stomach, red, sore tongue, and cheilosis. Later he developed ulcers of the stomach. The mother, since 1938, has complained of her stomach and has often had deep, red, cheilotic lesions. The descriptions of the children's conditions in many ways follow such an identical pattern that they may be grouped together.

All of the children were breast-fed babies until they were 18 months to 2 years old. With the exception of one of the girls, none of them was given any

supplement. This girl received orange juice and "blood tonic." Each child in turn was given butterbean soup "to start real eating." As small children they were all easily fatigued, had frequent headaches, severe muscular cramps in the legs, frequent cheilosis and injected eyes, constant mild colds and runny noses, and most of the time fretted and cried and slept fitfully. The social service workers have noticed that the two girls who did not receive treatment in the clinic were often cross and irritable, too.

The family picture is more one of simple nutritive failure than of specific organic defects. One of the boys has suffered from asthma since he was 2 years old. His physical condition seemed worse than that of the others. The children differ in the intensity of their signs and symptoms of nutritive failure, but the younger children are not necessarily in poorer health than the older children. One of the older boys has low-grade mentality.

Jean.—Jean was born March 18, 1933. She was delivered at term, after two or three minutes of labor. She weighed 7 pounds at birth. She cut her first tooth at about 4 months of age, sat alone at 6 months of age, walked at about 1 year of age and talked at about 18 months of age. She had pertussis at 3 months of age.

As a small child she was said to be emotionally very unstable. She complained of pains in her legs and burning in her stomach, and had frequent headaches, colds, and cheilosis. When she first came to the clinic as a patient in June, 1938, she had severe cheilosis and her eyes were injected. The family diet at the time was so deficient that Jean could not possibly have been getting enough food had her appetite been good, and it was not. Her two meals a day included butter beans, salt pork, bread, and milk and egg occasionally.

From June, 1938, through 1945, she was treated on numerous occasions with riboflavin. When she was just 12 years old she was included in an experimental study of the effects of milk upon growth of children. In this experiment no prescribed correction of the family diet was made in order to focus attention on the effects of the milk supplement.

Jean immediately began to grow taller and to fill out, and by the time she had been drinking milk for fourteen months she changed from a scrawny, thin girl to a well-developed adolescent. Her energy and appetite increased, and she had fewer lesions. When the milk was stopped, her lesions returned promptly. The following summary of her physical condition was made at the time she discontinued drinking milk:

JEAN'S CASE HISTORY

Date of examination: Aug. 8, 1946

Examining Physician: Esther Gross, M.D.

Interval History.—Patient has had no illnesses during the past year. She missed fifty-five days of school but not because she was ill. She is now assuming the rather difficult behaviorisms of a poorly adjusted adolescent. Her difficult attitude is being reflected in all the younger siblings. Menarche occurred on Jan. 13, 1946, and menses are now regular and uneventful.

Physical Examination.—Patient is 13 years, 4 months, 20 days old, weighs 88 pounds, and is 152.8 cm. tall. Pulse is 96 and blood pressure is 104/50.

She is fairly well developed and fairly well nourished. Previously she had been thin and underdeveloped physically.

Her head is not remarkable. Pupils are equal and react to light and accommodation. The conjunctivae are slightly injected. Sclerae and cornea show no changes. There is no photophobia as previously and the ophthalmoscopic examination is not remarkable.

The eardrums are intact bilaterally.

The nasal mucous membranes are reddened and the turbinates are swollen. This is about their usual condition.

The teeth are in good condition. The gums are slightly hypertrophied but are not reddened. There are well-healed rather deep scars at the angles of the mouth. The mucous membranes are shiny. The tongue is quite slick with a few deep fissures, and is slightly reddened at the tip. The tonsils are huge and cryptic. This is about her usual mouth condition except that on numerous occasions the lesions have been moist for long periods.

The cervical nodes are slightly enlarged, but there is no other lymph adenopathy as noted previously. The thyroid is now palpable.

There is no pallor of the skin, no edema, and no dermatitis. Axillary hairs are now present.

The chest is symmetrical and expands equally with inspiration. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs. The breasts are well developed.

The abdomen is at the level of the costal margins. It is soft and not tender to palpation. The liver and spleen are not enlarged.

The genitourinary organs have not been examined.

The extremities have never been remarkable.

The patient is intelligent and displayed no emotional instability during the examination. This is a radical change from her usual irritability and intractability.

The deep reflexes are equal and active bilaterally. Touch and vibratory sensations are intact. There are no motor weaknesses. Previously she had expressed and displayed muscular weaknesses.

The tuberculin patch test was removed by the patient, and the blood count was refused.

Comment: The patient is a fairly well-developed and fairly well-nourished 13-year-old girl, who is alert, cooperative, has good color, and appears to be in good health.

Garnie.—Garnie is the eighth child in the family. He was born Jan. 8, 1940. The family was on relief at the time and the mother's diet was restricted to butter beans, biscuit, and salt fat pork all through Garnie's babyhood. He was breast fed "whenever he wanted to," and had no other food except the juice of an orange once or twice a month. He cut his first tooth at 3 months of age and sat alone at 6 months. By the time he was 6 months old he had cheilosis at the angles of his mouth and injection of the lower lids. He had a profuse nasal discharge continuously. He walked at 11 months and talked at 14 months of age.

Garnie's mother states that he has never been really sick or "puny" in his life. As a small child he stayed in his mother's lap or "rode her hip" all of the time and screamed if he were taken away from her. He continued with a cold and cheilosis at frequent periods, and when he was seen in the clinic at 18 months of age he had raw red patches out from his nares over a wide area. Other children in the family had cheilosis simultaneously.

Between the time he was 18 months old and 5 years, 2 months old, he had recurrent colds, purulent nasal discharge, occasional fairly severe diarrhea, and he usually had lesions in and about his mouth whenever he was seen in the clinic. When he was between 4 and 5 years of age he was treated for riboflavin

deficiency. He was included in the milk study when he was 5 years, 2 months old. The following summary of his physical condition during the milk study was made in 1946:

GARNIE'S CASE HISTORY

Date of examination: Aug. 8, 1946

Examining Physician: Esther Gross, M.D.

Internal History.—Patient has had occasional upper respiratory infections but no other illnesses during the past twelve months. In May, 1945, he had a mild case of chicken pox.

Physical Examination.—Patient is 6 years, 7 months old, weighs 46½ pounds, and is 118.0 cm. tall. Pulse is 96 and blood pressure is 90/50.

He is well developed and well nourished now. A year ago he was fairly well developed but thin.

His head is not remarkable. The pupils are equal and react to light and accommodation. The conjunctivae are not injected, and the sclerae and cornea show no changes. There is no photophobia, and the ophthalmoscopic examination is not remarkable.

The eardrums are intact and have a good light reflex. In the past he has had occasional earaches and had otitis media when he was 4 years old.

The nasal mucous membranes are injected, and the turbinates are greatly enlarged. He has a chronic nasal discharge.

He has some dental caries and his oral hygiene is not good. There are a few well healed small scars at the angles of his mouth. At the junction between the upper lip and the gums on the left, there is a pea sized firm mass probably due to irritation from a ragged tooth. The mucous membranes are shiny. The tongue is finely granular with a few deep fissures, and is slightly reddened at the tip. The tonsils are moderately enlarged and cryptic but not injected.

There is moderate cervical lymph adenopathy, and the inguinal nodes are shotty. He has had cervical lymphadenitis occasionally, but no suppuration.

The skin is clear and the color is good. There is no edema of the skin and no dermatitis today, whereas, in the past he has had numerous lesions, and he has been pale.

The chest is symmetrical and expands equally with inspiration. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs. Previously he has had a slight sinus arrhythmia.

The abdomen is at the level of the costal margins. It is soft and not tender to palpation. The liver and spleen are not enlarged.

The genitourinary organs have not been examined.

The extremities are not remarkable.

The patient is fairly intelligent, and showed no emotional instability during the examination.

The deep reflexes are equal and active bilaterally. Touch and vibratory sensations are intact. There are no motor weaknesses.

The tuberculin patch test was negative a year ago.

The patient refused to have a blood count. A year ago his red blood cell count was 3.78 million and hemoglobin was 12.0 Gm., 78 per cent.

Comment: The patient is a well developed and well nourished 6 year old boy who is alert, somewhat rebellious, but appears to be in fairly good health.

INTERPRETATION OF RED GRAPHS OF JEAN AND GARNIE

The following interpretations of Jean's and Garnie's Red Graphs are offered. They have been made without referring back to the original roentgenograms in order to make a clear test of the graph itself.

Jean.—

Upper edge: Jean was on a slow schedule of bone development from 8 years to 12 years inclusive. She had an insidious slight retardation in her most

mature bones between 8 and 10 years of age, followed by a significant pause in bone formation for almost a year. She then recovered her former speed of bone growth in her most mature bones, and gained enough during the time she was getting the milk protein supplement to approximate the rate of one skeletal month growth for every month increase in her age. Apparently her hand was either fairly mature at the end of the milk study, or she had near optimum bone status, for her, in her most advanced centers. No "drop" in speed of bone production occurred.

Lower edge: Jean's bone was carrying a heavy, retarding load at 8 years of age. She reduced this load fairly rapidly even during the time between 10 and 11 years when little new bone was being deposited in her most mature bone centers. At the time she was put on the milk supplement, she had a fairly light retarding load and the skeletal part was developing fairly symmetrically. She was able to maintain this speed of bone growth, proceeding at a somewhat slow speed, after the milk protein was discontinued.

The zone: The curve for skeletal age (Todd) falls near the upper edge of the zone. Jean had much greater disturbance of bone growth before 8 years than she had between 9 and 12 years. Since she was able to reduce the width of the zone consistently, one would not anticipate that she had much skeletal anomaly or that the cause of the asymmetrical development of her hand was due to constitutional defects. This interpretation of her past health history before she was seen in the clinic is, of course, colored by the trend of the entire Red Graph, and at the time of her first examination at 8 years of age, one could say only that she was quite retarded in bone growth and was carrying a heavy retarding load in this region of the skeleton.

Garnie.—

Upper edge: The upper edge of the Red Graph is so far above the standard curve of reference that one immediately suspects a "runaway" type of bone development. No 3-year-old boy doubles his bone production without arresting one's attention. Apparently he has maintained this production consistently for the four and one-half years, confirming the "runaway" impression one would get at 3 years of age.

His speed of bone deposition has changed slightly recently, and one might make the statement cautiously that his skeleton is coming into a healthier state of equilibrium.

Lower edge: Garnie has some bones which are developing slowly and irregularly. These bones did not respond during the daily ingestion of the milk protein for over a year. Then they began to respond, but apparently they were not stabilized, for they lost some status as soon as the milk was stopped.

The zone: The nature of this area and the position of the curve of skeletal ages (Todd) confirm quite clearly the skeletal maturational disequilibrium suggested by the relation of the upper and lower edges to the standard curve of reference. This disequilibrium is still quite firmly entrenched, and a constitutional as well as environmental lack is suggested.

The facts are that Garnie does have a number of rare skeletal anomalies. He has more than one aberrant center of ossification which appeared ahead of schedule as well as a number behind schedule. His bone trabeculae are coarse, and he has heavy, closely spaced bone scars in the metaphysis of the radius.

In contrast, Jean has fairly fine bone trabeculae, no anomalies, and her few scars are not closely spaced. (See Fig. 5 on page 146 of the JOURNAL for two reproductions of her roentgenograms.)

SUMMARY

The Todd inspectional method of estimating the uniformity of maturation in regions of the skeleton has been reviewed, and a new graph for expressing the equilibrium of bone growth is described and illustrated. The authors have found the Todd inspectional method and this new form of graph useful in the clinic as aids in studies of nutrition and growth in health and disease.

The authors express their sincere appreciation to Dr. William Walter Greulich, Director of the Brush Foundation of Stanford University, Dr. Normand L. Hoerr, Professor of Anatomy of Western Reserve University, and Dr. B. Holly Broadbent, Director of the Bolton Study of Western Reserve University, for their permission to discuss this method prior to the release of the standards of reference for it. This condensed description of the graph has been made at the suggestion of the editors of the JOURNAL to clarify the article on page 137 of the JOURNAL.

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THE RED GRAPH AND THE WETZEL GRID AS METHODS OF DETERMINING THE SYMMETRY OF STATUS AND PROGRESS DURING GROWTH

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S. IDELL PYLE, M.S., CLEVELAND, OHIO, AND TOM D. SPIES, M.D.,
BIRMINGHAM, ALA.

SINCE 1940 the dynamics of growth in children with nutritive failure has been a major study in the Nutrition Clinic. A primary objective in this study has been to determine the effect of malnutrition on growth in children. Although there is no single method for measuring the two attributes of growth, increase in size and increase in cell complexity, in every type of body tissue,¹ an estimation of both attributes is vital for an understanding of the amount and the cause of nutritive failure in the young. There are chemical² and roentgenographic³ techniques for differentiating between them in bone and in soft tissue. The preferred method in the chemical and roentgenographic techniques is to measure the speed at which a child is developing in terms of maturity indicators^{1, 2, 4} rather than in terms of bulk or size. Maturity indicators are either the features of a body part and the secretory products of the cells of the part, or new phases of functioning that are attained in specific order.¹ They serve to identify the stage of cell differentiation which the organ or the part has attained.

Indicators have been described both for single organs or anatomic systems and for the entire body.^{2, 3, 5, 6} Of those available to date, the indicators described by Todd¹ and Wetzel⁶ have been used in the Nutrition Clinic for charting bone growth and general body growth, respectively. Both concepts treat growth as a process of progressive tissue maturing which has a universal *order* of change but a highly individualized *speed* of change. The Todd standard makes the speed of cartilage replacement by bone dynamic by timing the first appearance of the successive features of the child's joint surfaces and relating them to his age. The Wetzel Grid charts the growth for the body as a whole by first condensing the child's current stature and weight into (a) developmental levels (body size), and (b) physique channels (body build), and then by relating developmental levels with age to indicate speed and schedule of body development.

By the Todd method, the stage of development of the skeletal area chosen, e.g., hand, is determined according to the speed of maturing of each bone in that area by comparison with a standard series of skeletal maturity indicators. In order to obtain what is known as skeletal age (Todd) each bone is assigned an age, and the assigned ages are averaged.* Comparison of skeletal age with

Northwestern University Studies in Nutrition at the Hillman Hospital, Birmingham. From the Department of Nutrition and Metabolism, Northwestern University.

These studies were supported by grants from the American Dry Milk Institute, Inc.

*While it is clear that skeletal age (Todd) used in the literature is not an expression of age as he defined it originally,² no change in the current method of assessing skeletal age as it was done in the Brush Foundation Laboratories, Cleveland, Ohio, has been made in this study.

chronological age thus offers a condensed and practical measure of the skeletal development of the child.

In the Wetzel technique, a developmental age may be obtained by reading the chronological age on the Grid at which the 67 per cent auxodrome intersects the developmental level which the child has attained. By referring the child's developmental age so obtained to his chronological age, his degree of advancement or retardation with respect to the general population is expressible as a developmental ratio. A child who follows the 67 per cent auxodrome will have a "straight line" curve coinciding with the central-diagonal line in Figs. 1 to 4.

In health, skeletal maturing and general body maturing are so nearly parallel that they have been regarded as almost interchangeable.⁷⁻¹¹ Todd, however, regarded maturational level in bone as a "third measure of physical developmental growth during childhood, the other two being weight and stature."¹² In the Wetzel technique only two of the three measures, that is, height and weight (with age), are included. Wetzel states that developmental age "serves the same purpose as, but avoids the disadvantages connected with, roentgenologic determinations of skeletal age."¹²

When, however, skeletal age (Todd) was compared with developmental age (Wetzel) in 250 children in whom bone growth and general body growth were always studied in conjunction over a six-year period, it was noted that the two measures of maturity were not parallel or identical except in a short age range extending from 10 years, 4 months to 12 years, 8 months (Figs. 1, 2, 3, and 4). The results suggested that measures of maturation based on averages such as skeletal age (Todd) or on probability,¹³ such as developmental age (Wetzel), give a limited portrayal of the stage of development of a child at any given time. Nutritive failure affects the growth and differentiation of every cell in the body to some extent, as all cells are more or less dependent upon the food intake of the individual for growth and repair. It is also axiomatic that not all cells or tissues are mobilized simultaneously and to the same extent for maintaining the essential life processes, and that in times of prolonged stress such as nutritive failure certain cells or tissues take precedence in their demands over others. The ultimate result is a degree of asymmetry which is masked when growth is evaluated as an average or when it is based on probability no matter how small.

The writings of both Wetzel and Todd indicate that they were both cognizant of the shortcomings of condensed expressions of maturity. Wetzel states, "There is nothing in the definition of developmental age or in the method of determining it which could be construed to imply that equal developmental ages imply equal maturity or, more broadly, that developmental age is an unqualified measure of maturity."¹³ Todd pointed out his reservations when he said, "Until one realizes that maturity status does not correspond with stature or with weight and does not even necessarily correspond with age, that, indeed, it is governed by influences distinct from those which control either stature or weight, one is liable to expect that maturity rating should correspond in some degree with the ratings on age, on dimension, and on weight. Children of small stock may be adequately matured (in skeleton) though below average in stature. Children with families in which corpulence is characteristic may seem to be overweight but are not necessarily advanced in maturity rating."¹³

The desire to express the extent of symmetry of growth of the individual child on a biological rather than a mathematical basis has stimulated the authors to make use of those aspects of both the Wetzel Grid and the Todd roentgenographic technique which apply to the single child rather than to the group. The Red Graph method,¹ which is derived from the Todd method, and the Wetzel Grid both can be applied for this purpose as measures of the growth of an important tissue of the body and of the body as a whole, respectively. They are similar enough in concept and different enough in the facts revealed to be used in conjunction, for when Todd's and Wetzel's formulations are placed side by side the following similarities are noted (Table I):

TABLE I

IF ONE SEEKS	IT IS EXPRESSED IN THE WETZEL GRID BY:	IT IS EXPRESSED IN THE ROENTGENOGRAM BY:
Physique	Channel*	The contour', form', size-for-age and the internal architecture of the bone; amount of overlying tissue*
Nutritional grade	Adherence to preferred channel	Bone density, smoothness of bone margin, uniformity of the trabeculae according to the characteristics of the bone in question*
Developmental level	Child's current level in channel system*	Child's skeletal maturity plotted according to an oblique straight line (age scale)*
Progress	Character of channel course and of own auxodrome	Progress denoted by the area between the most advanced and least advanced levels of maturity in the skeleton (i.e., Red Graph)*
Evidence of unsatisfactory variation in physical status	Cross-channel deviation toward left or right, and as a rule, slow down in auxodromic progress	New and old bone scars; difference in density of diaphyseal and metaphyseal bone; relative maturity and density of the secondary centers of ossification according to the order in which they begin to ossify*
Disturbance of growth	Cross-channel deviation; auxodromic lag	Bone scar, difference in bone density and architecture of the metaphysis*
Predicted basal heat	Caloric level chart aligned with developmental levels*	Equivalent unknown: possibly the upper edge of the Red Graph*
Load imposed by growth failure	"Calorie debt" and "growth debt" to be calculated from level difference between expected and actual auxodromes	Rate of deposition of bone: development of joint surfaces, to be gauged by the least advanced and most advanced bone maturity indicators*
A measure of comparative advancement	Developmental age (Wetzel)*	Skeletal age (Todd)*

*These parts of the analysis of the child's growth can be made at the initial examination or any one subsequent examination of the child.

Fig. 5, which will be discussed presently, shows what the authors have found to be the minimum essential data necessary for an interpretation of the Todd and Wetzel formulations. The following Comparative Charts I and II for two girls, Jean and Betty, are derived from all of their data collected during the milk study, and are based on the preceding comparisons of the Todd and Wetzel formulations. The details of Jean's medical history are presented on

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CHART I. COMPARATIVE CHART FOR JEAN

Birth date: March 18, 1933		Age at beginning of milk study, 12 yr Age at end of milk study, 13 2 yr.
JEAN'S	ACCORDING TO THE GRID	ACCORDING TO THE ROENTGENOGRAMS PLUS THE RED GRAPH
Physique	Fair throughout	Long slender bones: fairly dense → quite dense
Nutritional grade	Optimum throughout	Fair → good
Developmental level	92 → 111 (in 14 mo)	At least 10 months behind schedule → at least 3 months behind schedule
Progress	Adhered to own channel course. Adhered to own auxodrome with abrupt slowing last two months of milk study	Slow with fairly heavy load → a little slow with moderate load
Evidence of unsatisfactory variation in physical status	No evidence in channel course; variation in auxodrome during last 2 months of study	5 old scars, many fine scar remnants → 2 recent scars, some remnants
Disturbance of growth	1 deviation (not significant) Slight auxodromic lag last 2 months	Diffuse increased density, smooth, dense bone texture; 2 recent scars
Predicted basal heat	1,138 calories → 1,230 calories	—
Load imposed by growth failure	Essentially no debt	A year retarded with nearly a two year retarding load → ¾ year retarded with a little less than a year retarding load
A measure of comparative advancement	1.8 yr. retarded → 2 yr retarded	1 3/4 yr retarded → very little retardation

CHART II. COMPARATIVE CHART FOR BETTY

Birth date. Sept. 13, 1933		Age at beginning of milk study, 11.5 yr Age at end of milk study, 13 2 yr
BETTY'S	ACCORDING TO THE GRID	ACCORDING TO THE ROENTGENOGRAMS PLUS THE RED GRAPH
Physique	Borderline → poor → borderline → poor	Thin, small boned → thin, significant increase in size
Nutritional grade	Below optimum throughout	Poor → only fair
Developmental level	68 → 92 (in 20 mo)	At least 12 yr. behind schedule → at least 8 mo behind schedule
Progress	Drift toward less favorable channel course. Smooth, insidious slowing of auxodrome	Slow with heavy load → slow with moderate load
Evidence of unsatisfactory variation in physical status	Cross channel deviation 3 times, once significant, accompanied by insidious slowing of progress	1 old thin scar, 1 new heavy scar, many light old remnants → 3 heavy scars, few light old remnants
Disturbance of growth	1 significant disturbance; slight lag in progress	1 scar, diffuse increased density during milk study
Predicted basal heat	1,032 calories → 1,138 calories	—
Load imposed by growth failure	Essentially no debt	Over a year retarded with a 2 year retarding load → about a year retarded with slightly less than a year retarding load
A measure of comparative advancement	2 1/2 yr. retarded → 3 1/2 yr. retarded	2 0 yr retarded → 7 months retarded

page 132 of the JOURNAL. Betty's medical history is summarized in the Appendix of this paper

DISCUSSION

An attempt has been made to compare the Red Graph formulation and the Wetzel Grid formulation for similarities and differences in quantifying growth.

COMPARISON OF SKELETAL AGE (TODD)* AND DEVELOPMENTAL AGE (WETZEL) IN 250 CHILDREN

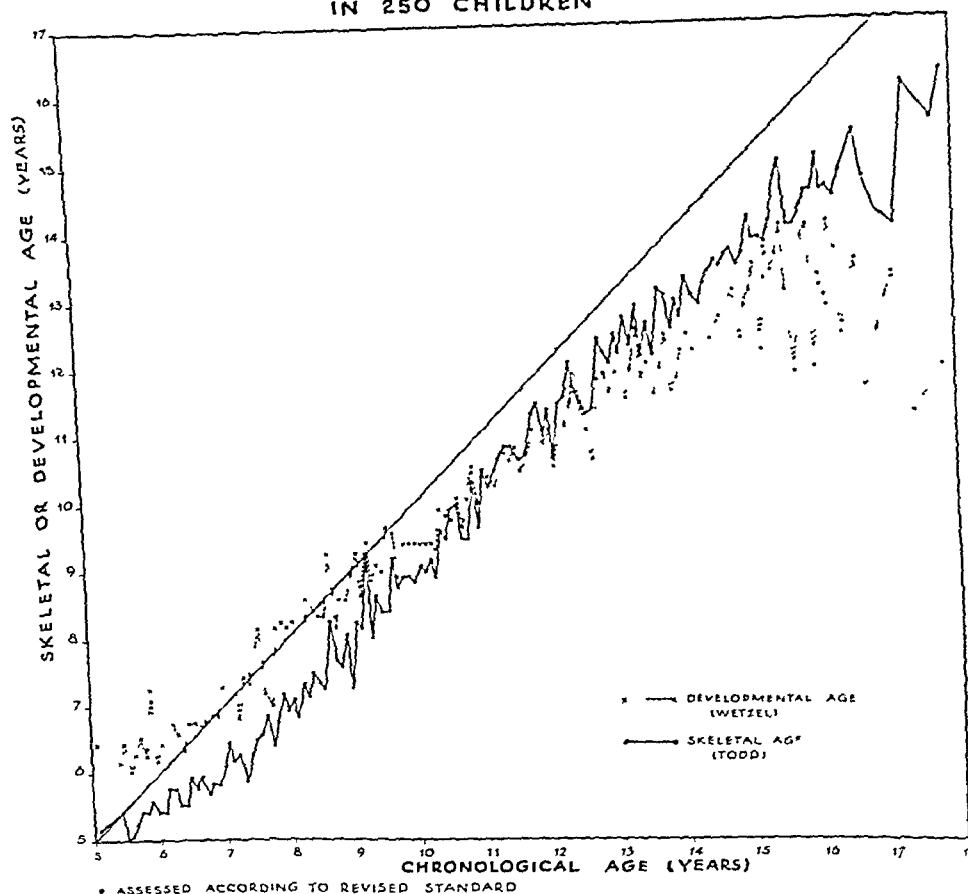


Fig. 1—In 250 children used for comparative purposes, skeletal age (Todd) and developmental age (Wetzel) are not parallel or identical except over a very short age span. Every child was included more than once at a number of evenly spaced successive ages. A child's developmental age (Wetzel) was never plotted without the corresponding skeletal age (Todd).

and for their application as indicators of the growth of a body part and of the body as a whole, respectively. In a previous report the authors have expressed the desirability of supplementing the Wetzel Grid with other devices such as

roentgenograms to measure growth.¹⁴ The desire stems from the need for an understanding of the functional and structural symmetry of the parts and of the body as a whole. Neither the Todd method nor the Wetzel method was

**COMPARISON OF SKELETAL AGE (TODD)*
AND
DEVELOPMENTAL AGE (WETZEL)
IN 141 GIRLS**

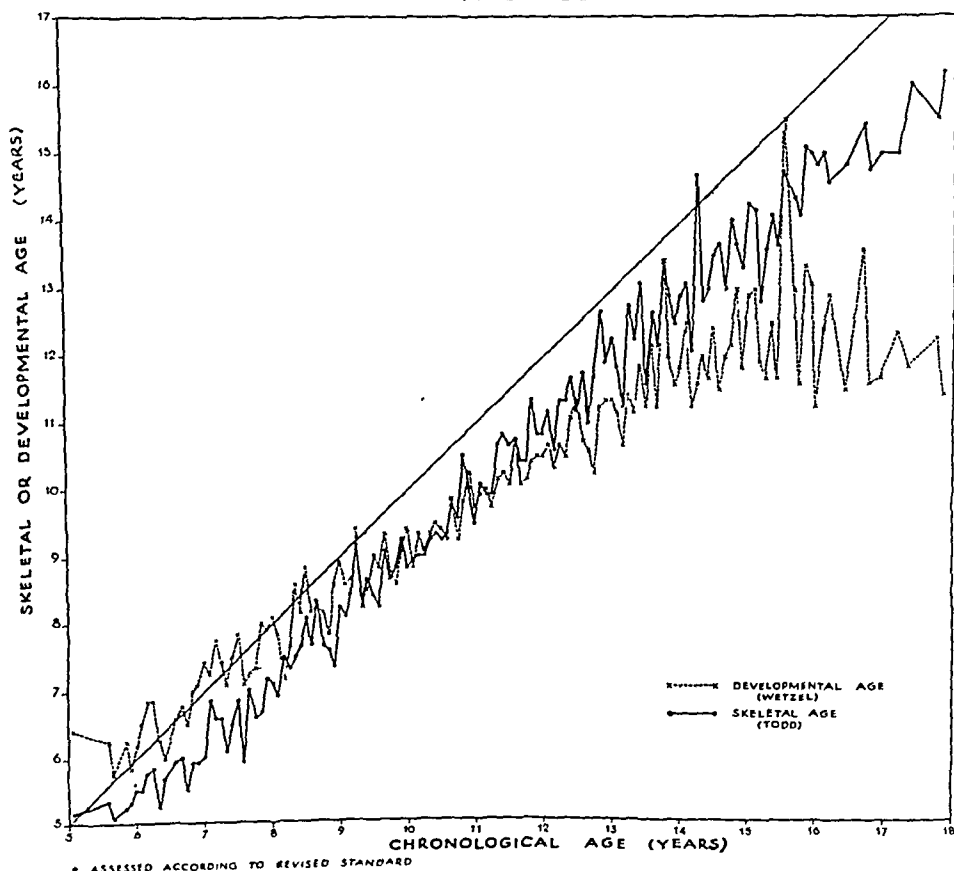


Fig. 2.—In 141 girls skeletal age (Todd) and developmental age (Wetzel) were not parallel or identical except over a very short age range.

proposed as an end in itself, but as a means of analyzing the functional status of the part and of the whole from the structure attained by the part and by the whole.

In a review of the Wetzel Grid it has been stated that "Children on the same level lines [i.e., developmental levels] thus all have the same surface area even though they are of different body shapes, that is, even though their points

are found in different channels."¹⁵ It follows therefrom that children with identical surface areas have identical basal caloric needs according to the Wetzel Grid. Having identical surface areas does not reveal, however, whether two children have progressed to the same stage of maturation. Although identical developmental levels (Wetzel) indicate that two children probably have the

**COMPARISON OF SKELETAL AGE (TODD)*
AND
DEVELOPMENTAL AGE (WETZEL)
IN 109 BOYS**

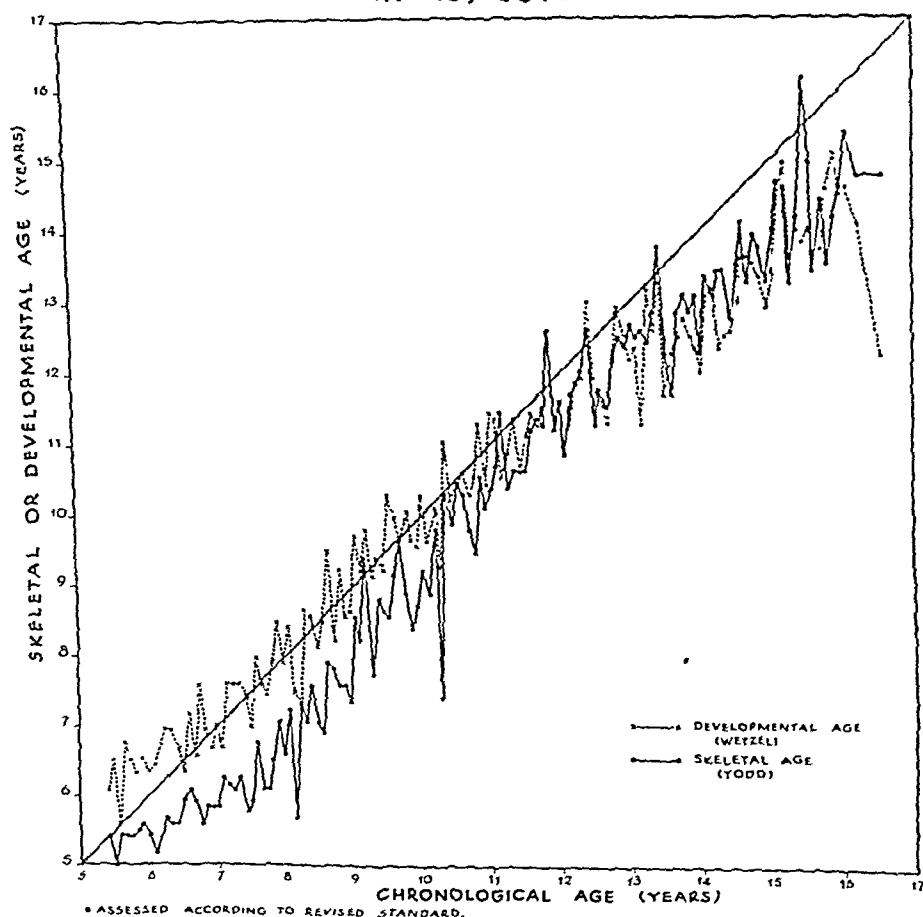


Fig. 3.—In 109 boys skeletal age (Todd) and developmental age (Wetzel) are not parallel or equal except over a short age range. The divergence of the two curves in the upper age range, however, is not nearly so great as it is for the girls.

same caloric needs, the two children may differ in their requirements for the various specific nutrients because they are at different stages of maturation.

Fig. 5 illustrates how two girls, Betty and Jean, who are nearly the same chronological age and according to their Grids, were of similar body shape

(physique) until Jean's pubescent changes began, were, according to their roentgenograms and their secondary sex characteristics, at different stages of skeletal maturation. While their diets in general differed considerably, they were both

SEQUENTIAL DEVELOPMENTAL AGES (WETZEL)
AND SKELETAL AGES (TODD)
FOR CHILD NO.74

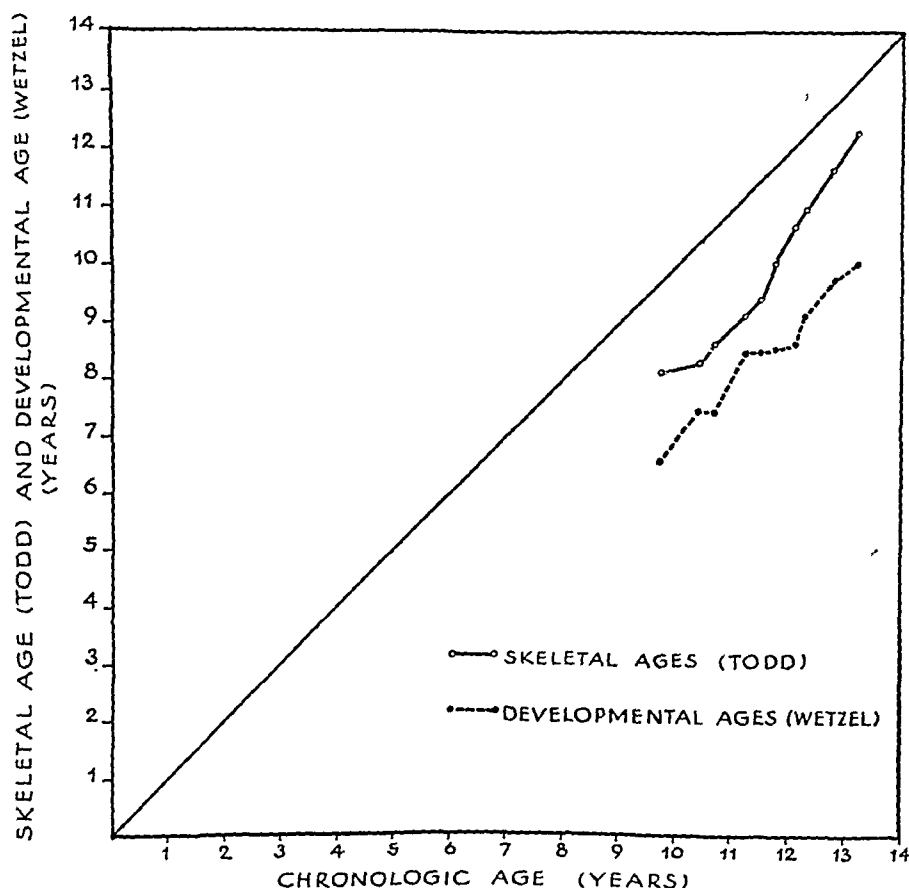


Fig. 4.—Betty's sequential skeletal ages (Todd) compared with her sequential developmental ages (Wetzel). The two ages are not interchangeable. The two curves suggests that one or combinations of the three over weight and living bone, become, operative in different ways at 131 in the JOURNAL for Jean's skeletal age curve [Todd]).

in a continuous state of nutritive failure for different causes. The response of Jean and of Betty to the same amount of milk supplement was so different that it appears illogical to attribute it to the fact that Betty needed more calories than Jean. In the light of her history, Jean's change in channel position and

the continued upward trend of her auxodrome must be attributed to a combination of the pubescent changes and the effects of the milk supplement. Jean's Grid curves do not, however, indicate clearly to which degree the changes were pubescent and to which degree they were nutritional in causation. On the contrary, the skeletal maturity indicator of pubescence, namely, epiphyseal fusion,¹⁶ is seen in Jean's roentgenograms and the secondary sex changes of the pubescent stage are obvious in her photographs. The roentgenogram and the photographs reveal growth facts to the authors which the shape of her auxodrome alone does not reveal, as the auxodrome does not show the post-pubescent levelling.

The analysis of the data presented in Fig. 5 suggests that there is a need for distinguishing between the specific nutritional requirements of Betty and Jean; their caloric needs were repeatedly the same according to their Grids, but they were at different stages of maturation according to their skeletal and gonadal indicators. From the standpoint of specific nutritional requirements, our clinical problem centers in the functional symmetry of the various parts. (The symmetrical structural maturation of the parts of the body depends upon functional symmetry.) The concept of functional symmetry is fundamental to the full understanding of skeletal growth, and the Red Graph formulation appears to the authors to offer a method, however crude at this stage, whereby the symmetry of maturation may be quantified.

SUMMARY AND CONCLUSIONS

Clinical use of height and weight, photographs and bone roentgenograms in the analysis of nutritive failure in children has been discussed, and a Comparative Summary Chart for clinical use has been presented. Height and weight were reduced to graphic form by the Wetzel method. The roentgenograms were interpreted graphically by the Red Graph method. The Red Graph is based on the Todd formulation, and it offers a method whereby the symmetry of skeletal status and progress during growth may be quantified. The following conclusions have been reached:

1. Developmental age (Wetzel) derived from the Grid and skeletal age (Todd) derived from bone roentgenograms were seldom identical, and are not always interchangeable as measures of the stage of maturation which a child has reached when his own mode of progress is considered.
2. Developmental age (Wetzel) and skeletal age (Todd) are expressions of growth symmetry when referred to the child's age.
3. Comparison of a child's auxodrome and his Red Graph aids in visualizing the developmental symmetry of his body in relation to his skeleton.
4. The Red Graph and the channel and auxodrome curves derived from the Wetzel Grid may be used independently. When the authors have used the Wetzel Grid and the Red Graph method in conjunction, more of the developmental interrelations of bone and of the soft parts have been revealed.

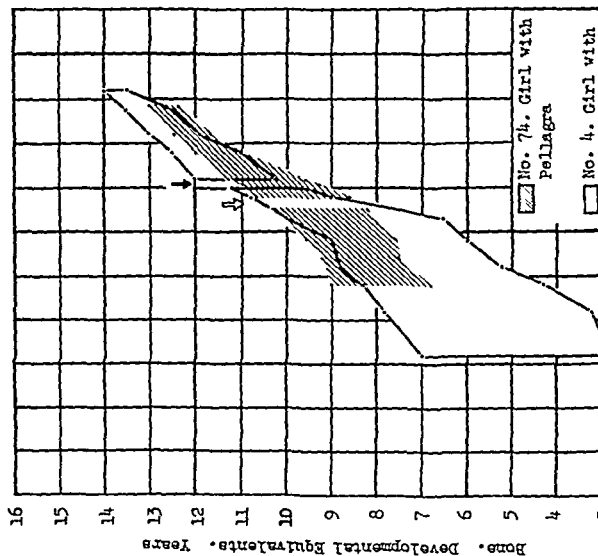
Fig. 5.—Photographs, roentgenograms, Grid curves, and Red Graphs for Jean and Betty. The two photographs and the two roentgenograms selected for each girl were taken at the beginning and the end of the milk study. The Weitzel Grid and Red Graph cover the whole period during which the girls have been under clinical observation. Jean was 12 years old and Betty was 11 years, 2 months old when the milk study was started, but both were 13 years, 2 months old when they discontinued drinking the milk supplement. Some of the points indicated to the writers by this figure are:

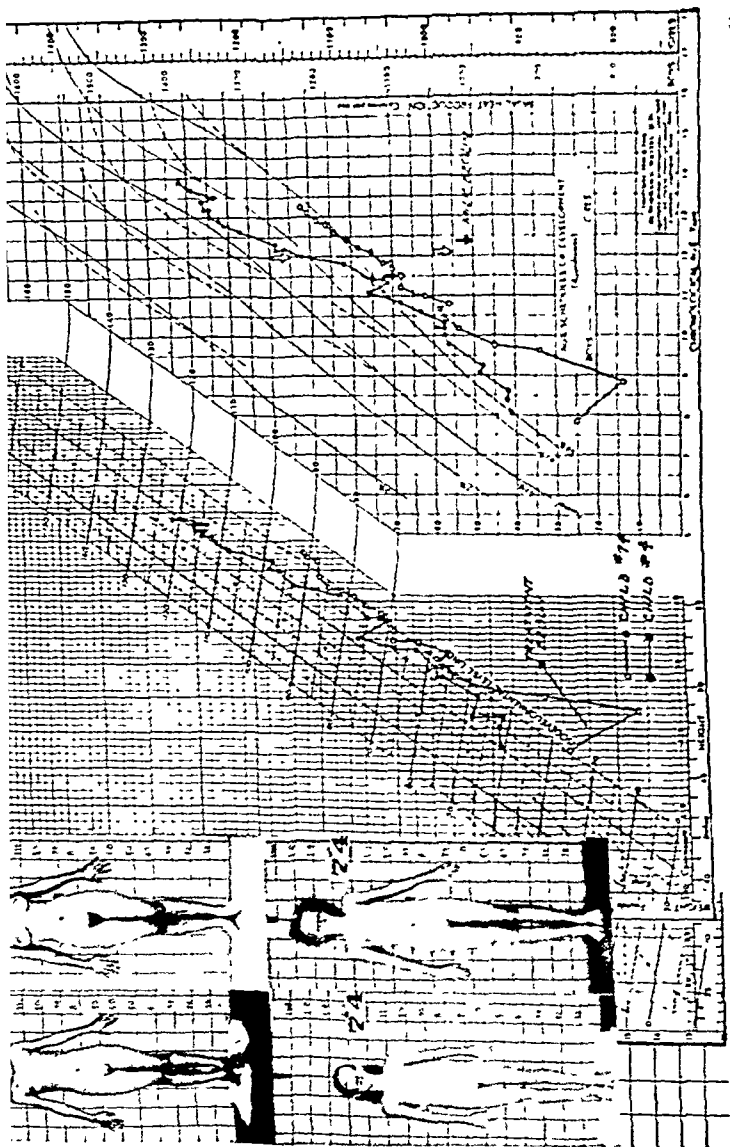
1. The four photographs reveal differences in the maturity of the secondary sex characters and differences in the body build. Jean attained her menarche nine months after the first illustrative photograph was made, when she was 12 years old. Betty has not yet attained her menarche, at 11 years, 2 months.
2. Betty's roentgenograms reveal no epiphyseal-diaphyseal fusion in any of the distal phalanges of her left hand. Jean's roentgenograms, however, show that the epiphysis of the distal phalanx of the thumb has begun to fuse with its diaphysis. Jean's hand, therefore, had the skeletal puberal indicator close to her menarche, and Betty's hand is clearly not as advanced. Betty's roentgenograms reveal a significant increase in the size of her hand, whereas Jean's roentgenograms show proportionately less change in her bone size. The nature of the change in the growth of Betty's hand confirms the epiphyseal indication that she was not as mature skeletally as Jean.



BONE GROWTH

Two Girls, Matched According to Bone Maturity Indicators.
Approximately Same Chronological Age





3. The two Red Graphs, derived from all of the roentgenograms of the two girls, show that Jean carried the greater retarding load until the milk supplement was begun. Comparison of the upper edges of the two Red Graphs indicates to the writers that the two girls developed their most mature bone at nearly the same speed. Jean responded promptly during the administration of the milk supplement by increasing her speed of bone production. Betty did not change her maximum speed of bone production very much, but she reduced her retarding load more significantly than Jean did.

4. Jean was changing her channel position to that which she followed during the milk study just at the time the study was beginning. However, she moved up-channel with less fluctuation, substituting quite clearly the clinical diagnosis that her health improved. In contrast, Betty moved into a less favorable channel position although her osteogenic progress was smoother. This is not in agreement with the clinical findings of improvement in her health and energy.

5. When these roentgenograms, photographs, Grid curves, and Red Graphs were considered simultaneously, a distinction could be made by the pubertal changes and changes due to improved nutrition. The Grid curves alone do not reveal this point clearly to the writers. The Red Graph alone is not intended to reveal when changes like puberty occur unless the proper skeletal indicator is indicated in the graph.

APPENDIX

SUMMARY OF BETTY'S MEDICAL HISTORY

Betty was born Sept 13, 1933, and is the youngest of five children. Her mother is living and well, her father died in 1941 of a brain tumor. Her brother and three sisters range in age from 18 to 29 years. Her brother was rejected from the army because of poor health and "small" size. Her sisters have been patients in the Nutrition Clinic.

Betty weighed 6½ pounds at birth. She was delivered at term after three hours of labor. She did not cut her first tooth until she was one year old. She sat alone at one year of age, and was walking and talking at 2 years of age.

She had pellagra and rampant dental caries when she was examined in the clinic for the first time in 1941. She was described then as a small, very emaciated child who looked pale and wan. From that time until she was given the milk supplement daily, she was treated intermittently for pellagra followed by generalized nutritive failure because of incomplete recovery from pellagra.

Betty's appetite has never been very good. When the milk study began, she was usually eating only two meals a day. Breakfast often consisted of bread and butter, gravy and a piece of white meat, and water to drink. Supper consisted mainly of dried butter beans, sometimes she had mashed potatoes. She had milk about three times per week and some fresh fruit in season. She ate lots of candy.

Past Illness History—This history was obtained from the mother and the patient. Betty's mother is very pleasant, and gives a fairly reliable history.

At 2 years of age, mumps, no complications.

At 3 years of age, chicken pox, no complications.

At 8 years of age, pellagra, followed by general nutritive failure because of incomplete recovery from pellagra.

At 9 years of age, measles, no complications.

pneumonia, marked cervical adenitis, delirium and high fever, ill for three months.

At 10 years of age, ariboflavinosis and recurrent pellagra, followed again by general nutritive failure because of incomplete recovery from pellagra.

The following clinical notes by Dr. Esther Gross and Dr. Arvin W. Mann indicate her status at the beginning of the milk study, when she was between 11½ and 12 years old:

General Appearance, April, 1945—The patient is a fairly well developed, rather thin, very talkative child who appears to be in fair health except for dental caries and myopia which has been corrected with glasses for about one year. No definite form of deficiency disease is now indicated, but she has generalized nutritive failure. She has frequent diarrhea, questionable asthma, and she has a cold almost all of the time. She has a headache "off and on." The patient gives the impression of being emotionally unstable, and says she thinks she is. She failed twice in the first grade but likes school, and is doing well now in the third grade.

Physical Examination, July 25, 1945—Pulse is 90, blood pressure is 108/70. Her pupils are equal and react to light and accommodation. Conjunctivae and sclerae are not injected. She has no photophobia, and the ophthalmoscopic examination reveals no abnormalities. The left eardrum is obscured by dark, hard cerumen. The right drum is not injected, and has a good light reflex. The nasal mucous membranes are injected, the turbinates are swollen and there is a small amount of mucopurulent discharge present.

She has extensive dental caries, and oral hygiene is not good. The lips are mottled, but she has no cracks or ulcers. The gums are hypertrophied and slightly reddened. The angles of the mouth are clear. The tongue is slick at the edges, and slightly red at the tip. The tonsils are cryptic. The anterior cervical lymph nodes are enlarged, the inguinal nodes are shotty. The skin is clear.

Her chest is symmetrical and expands equally with inspiration. There is no beading of the ribs. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs.

The abdomen is at the level of the costal margins. It is soft, not tender to palpation, and no masses are found. The liver is at the level of the costal margin. The spleen is not enlarged. The costovertebral angles are not tender to pressure.

The extremities are not remarkable. The deep reflexes are equal and slightly hyperactive. Vibratory and touch sensations are intact. The patient gave the impression of being somewhat emotionally unstable.

She was placed on a dietary supplement of one quart of reconstituted, dry, defatted milk six days a week from April, 1945, through November, 1946. In view of the unfavorable change in channel position on the Grid, a detailed medical examination was made on June 13, 1947, six months after the milk was stopped. The findings were as follows:

Interval History.—Patient was ill twice during the past year with fever, sore throat, and swollen cervical lymph nodes. She missed two weeks of school. She passed to the senior fourth grade. She has easy fatigability, very occasional headaches, no burning or injection of the eyes, no blurred vision, and no night blindness. She has had no trouble with her ears. She has had no epistaxis. She had ulcers in her mouth several times during the year. She had no burning of the skin and no dermatitis. Her appetite has been good. She has had no vomiting, constipation, or abdominal pain, but has had occasional bouts of diarrhea which last three or four days, the last occurring about two weeks ago. She has had no symptoms referable to the genitourinary tract. She has no trouble sleeping, but is nervous and gets angry easily.

Physical Examination.—The patient weighs 76 pounds and is 151.4 cm. tall. Her pulse is 108, and her blood pressure is 112/62. She is fairly well developed and fairly well nourished.

Her head is not remarkable. The pupils are equal and react to light and accommodation. The conjunctivae and sclerae are not injected. The cornea is clear. There is no photophobia, and the ophthalmoscopic examination of the fundi shows no changes. The left drum is obscured with dark, tarry looking wax. The right drum is intact and has a good light reflex. The nasal mucous membranes are not injected.

Some of the teeth are quite carious, all are badly stained, and oral hygiene is poor. The gums are hypertrophied, reddened, bleed easily, and are receding. The lips show no changes. There are old deep scars especially prominent at the left angle of the mouth. The tongue is coarsely granular and all the papillae are quite prominent. The tonsils are enlarged.

The cervical lymph nodes are moderately enlarged, and the thyroid is just palpable.

The patient has many freckles but the texture of the skin is good. There is slight pallor, but no edema of the skin and no dermatitis.

The chest is symmetrical and expands equally with inspiration. The breasts are beginning to show slight development. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs.

The abdomen is at the level of the costal margins. It is soft and not tender to palpation. Liver and spleen are not enlarged. There are no masses. The costovertebral angles are not tender to pressure. Pubic hair is present and axillary hair is just starting. The patient has not yet menstruated.

The extremities are not remarkable. The patient displayed no emotional instability during the examination. The deep reflexes are equal and active bilaterally. Touch and vibratory sensations are intact. The tuberculin patch test is negative. The red blood cell count is 4.77 million. Hemoglobin 13.2 Gm., 85 per cent.

Comment.—The patient has gained 13 pounds and 12.5 cm. in height during the twenty-month period of milk ingestion, and has gained 7.5 pounds in the last six months. She is a fairly well-developed, fairly well-nourished 13-year-old girl who is cooperative, pleasant, and in moderately good health. She has a slight speech defect.

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At 9 years of age—measles, no complications; pneumonia, marked cervical adenitis, delirium and high fever, ill for three months.

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Her chest is symmetrical and expands equally with inspiration. There is no heaving of the ribs. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs.

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Some of the teeth are quite carious, all are badly stained, and oral hygiene is poor. The gums are hypertrophied, reddened, bleed easily, and are receding. The lips show no changes. There are old deep scars especially prominent at the left angle of the mouth. The tongue is coarsely granular and all the papillae are quite prominent. The tonsils are enlarged.

The cervical lymph nodes are moderately enlarged, and the thyroid is just palpable.

The patient has many freckles but the texture of the skin is good. There is slight pallor, but no edema of the skin and no dermatitis.

The chest is symmetrical and expands equally with inspiration. The breasts are beginning to show slight development. The lungs are clear to auscultation and percussion. The heart is not enlarged, the rate is normal, the rhythm is regular, and there are no murmurs.

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DO ERYTHROBLASTOTIC NEWBORN INFANTS DESTROY Rh-NEGATIVE RED BLOOD CELLS?

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FOR the past several years infants with erythroblastosis fetalis have been treated with multiple transfusions of Rh-negative blood. More recently, the procedure of exsanguination and replacement with Rh-negative blood has been used. Experience in patients requiring an even larger amount of Rh-negative blood has raised a question: Can this entire problem be answered by the replacement with Rh-negative blood?

During the past three years I have observed three infants with erythroblastosis fetalis who remained anemic despite transfusion with Rh-negative blood in the amount of twice their estimated blood volume.

One infant weighing 3,360 Gm. at birth received 880 c.c. of Rh-negative blood during the first six weeks of life. She was discharged from the hospital at that time with hemoglobin 63 per cent and red blood cells 3,350,000.

A second infant, who weighed 3,750 Gm. at birth, received 1,085 c.c. of Rh-negative blood during the ensuing six weeks. At the end of this time the hemoglobin was 74 per cent and red blood cells 3,990,000.

Questioning has revealed others who have had a similar experience.

Following is a report of a recent patient requiring a large amount of Rh-negative blood:

CASE REPORT

P. W., a white female infant, was the fourth child. Three siblings, aged 8, 6, and 4 years, respectively, were alive and well. The mother was Rh-negative and two days post partum her blood showed anti-Rh blocking antibodies in a titer 1:1,024 (anti Rh₀'). Labor was of six hours' duration, and the baby, weighing 2,730 Gm., was delivered by low forceps from a left occipitoanterior presentation. The infant cried promptly and seemed to be in good condition until the day after birth, when jaundice was observed. The infant was first seen by me on the third day of life. She was deeply jaundiced, apathetic, and listless. The liver was 3 cm. below the costal margin. The spleen was not felt. The hemoglobin was 54 per cent, red blood cells 2,730,000, white blood cells 37,500, and the smear showed 60 normoblasts per 100 white blood cells.

The baby was transfused daily for the next week, receiving a total of 315 c.c. Rh-negative blood. (Fig. 1) She was in good condition at that time, with hemoglobin 79 per cent and red blood cells four million, but ten days later the hemoglobin dropped to 53 per cent and the red blood cells to 3,290,000. From that time until discharge another 305 c.c. Rh-negative blood was given. (Fig. 1)

The baby was finally discharged at 6 weeks of age with hemoglobin 66 per cent and red blood cells 3,520,000, having received during that period a total of 620 c.c. Rh-negative blood.

DISCUSSION

Lucas and Dearing,¹ who contributed an early study on blood volume in the newborn infant, found the average to be 147 c.c. per kilogram of body weight. Bakwin and co-workers² in a later study found the blood volume in infants to vary between 71 and 148 c.c. per kilogram of body weight, with

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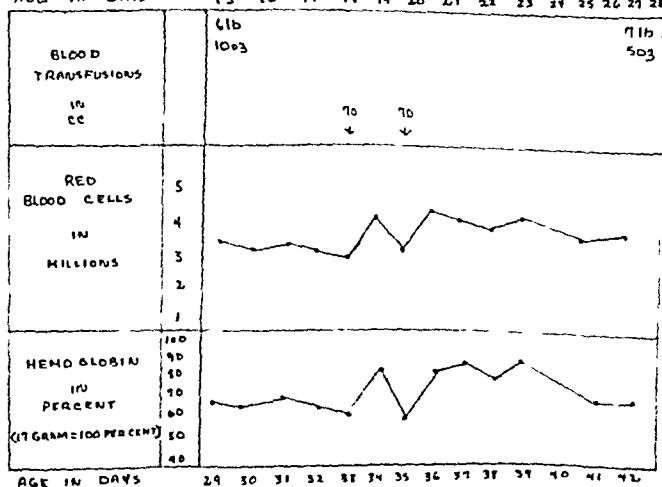
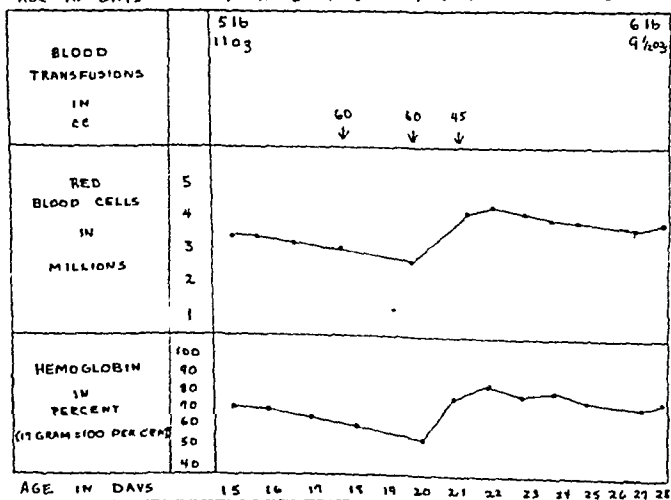
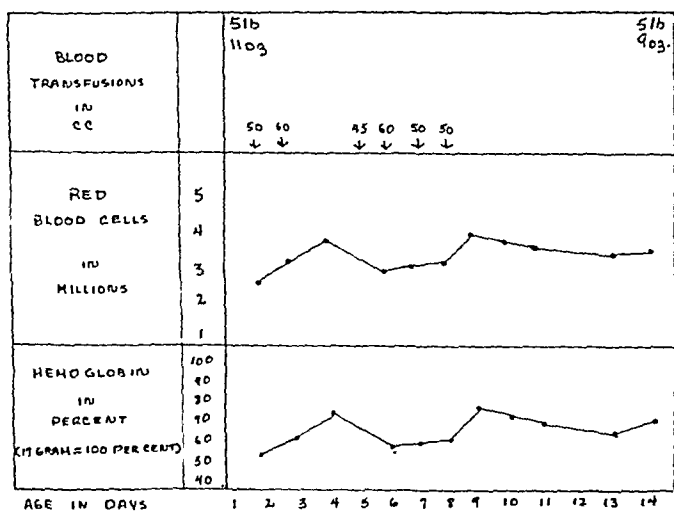


FIG. 1.

the higher figures in the newborn infant and an average of 101 c.c. These authors showed the decrease in the amount of blood per kilogram of body weight as age increases to be due to diminution in the volume of red blood cells. Wintrobe³ estimates the total blood volume at birth to be about 300 c.c., with gradual increase until it doubles at the end of the first year. These wide variations make accurate estimations difficult, but by any one of them the amount of blood given in the three reported cases approximates twice that of the estimated blood volume.

The normal newborn child has 4,800,000 to 6,200,000 red blood cells at birth, and this drops to a low point of 4,400,000 to 3,400,000 at 6 to 8 weeks of age.⁴

The blood used for transfusion in the first two reported cases was taken from the Medical College of Virginia Blood Bank and special effort was made to supply blood no more than five days of age. Blood for the case reported in detail was furnished by another blood bank, and the director has assured me that the rapid turnover almost precludes the use of blood older than five days. The blood was tested only with anti Rh₀ serum, so it may have contained Rh' and/or Rh'' antigens which would be subject to destruction by maternal antibodies. However, this is extremely rare.

Callender and co-workers⁵ have demonstrated the average life span of the transfused red blood cell to be sixty-three days.

In order for the red blood cell count of the reported patients to approximate a normal level, Rh-negative blood in the amount of approximately twice the estimated blood volume was necessary, and the average life of these Rh-negative blood cells should have been ample to span the six-week period of life reported.

According to Damashek,⁶ "the spleen is certainly of aid in most hemolytic processes, and at times initiates and carries through the entire reaction." It is possible that in these cases the splenic tissue is geared to excessive blood destruction and may overstep its balance and destroy some normal red blood cells.

SUMMARY

Three infants with erythroblastosis fetalis in whom twice the estimated blood volume was replaced with Rh-negative blood are reported. In view of the large amount of Rh-negative blood required in these three patients, the question is raised as to whether or not replacement of Rh-positive blood with Rh-negative blood completely answers the problem. The question is also raised as to the mechanism causing destruction of the Rh-negative red blood cells.

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NATURAL INCIDENCE OF INFLUENZA ANTIBODIES IN CHILDREN OF DIFFERENT AGE GROUPS

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ALTHOUGH the majority of adults have been shown to possess considerable quantities of neutralizing antibodies against the influenza virus, there is little available data about neutralizing antibodies in children of various age groups, as well as a paucity of data comparing influenza antibody levels of mothers and their infants.

It is the purpose of this paper to report the correlation between maternal and infant serum antibody levels, to show that the age groups up to 6 or 7 years of age are deficient in spontaneous influenza antibodies; and to reveal the unevenness of immune antibodies in the older age groups to different strains of the influenza virus.

Rickard and Horsfall¹ performed quantitative neutralization tests with influenza A virus and the serum of mothers and their infants at various periods after birth. They found that during the first two months of life infants possess antibody levels almost identical with those of their mothers. During the third and fourth months antibody levels rapidly decreased in infant serum, and from the fourth to the sixteenth month very few infants possessed demonstrable concentrations of antibodies against this virus.

Francis and Magill² showed that the frequency of completely protective sera in newborn infants is approximately the same as in middle-aged individuals. After the first month of life, a sharp drop in the percentage of positive sera occurred and persisted through the first year of life. After the first year of life the incidence of antibodies increased to its maximum between 20 and 40 years, when 90 per cent of the sera conferred complete or partial protection to mice infected with the influenza virus.

Andrewes and co-workers³ reported the incidence of neutralizing antibodies to human (Weiss strain) influenza virus as lower in children under 10 years of age than in older children and adults. Neutralizing antibodies to swine influenza were regularly found present in adult sera but were wholly absent from the sera of children under 10 years of age.

Serum was obtained from eighty-one children in the Pediatric Clinic of Beth Israel Hospital between October, 1946, and March, 1947. The ages of these children ranged from one month to 18 years. Serum was also obtained from thirteen mothers and their newborn infants.

METHODS

Serologic Tests.—For measuring the concentration of influenza antibody in serum, the red cell agglutination inhibition reaction⁴ was employed. The technique used was the modification of the U. S. Navy Laboratory Research

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Unit 1 method.⁴ Tests in the laboratory indicated that if these titers were multiplied by twenty-five they would correspond roughly to those reported by Salk and co-workers,⁵ where a correlation between influenza susceptibility and antibody level was found in man.

The strains of influenza virus employed in these tests were type A consisting of the PR8 strain and type B consisting of the Lee strain grown on chick chorioallantoic fluid.

The probable influenza susceptibility status of our group based on the study of Salk and co-workers⁵ is as follows:

<i>Susceptibility of Influenza</i>	<i>Titer Range</i>
Susceptible	< 8
Probably resistant	8-64
Almost certainly immune	> 64

The neutralizing capacity against the PR8 strain of the influenza A virus and against the Lee strain of influenza B virus of the serum of thirteen mothers and their newborn infants was determined. The results are presented in Table I. It will be seen that the distribution of antibody levels was only slightly different among mothers and their infants during the neonatal period. There was a slight tendency for the infant titers to be a trifle higher, with the exception of the two highest maternal titers.

TABLE I. RESULTS OF NEUTRALIZATION TESTS WITH INFLUENZA A AND B VIRUS AND THE SERA OF MOTHERS AND THEIR NEWBORN INFANTS

NAME	MATERNAL		INFANT	
	PR8	LEE	PR8	LEE
A.	2	2	4	2
B.	2	< 2	2.8	2
G.	64	< 2	45	2
L.	128	2	64	2
L.	< 2	2	2	2.8
M.	11.2	2	22.5	4
O.	4	< 2	2	< 2
P.	2	< 2	4	2
Re.	< 2	2.8	< 2	5.6
Rob.	2	< 2	2	< 2
Rod.	< 2	< 2	2	2
S.	< 2	< 2	2	2
T.	2.8	5.6	5.6	22.5
Total number	13	13	13	13
Average titer	16.7	2.3	12.3	4.1

In Table II it will be seen that there is a uniformly low distribution of antibody levels to both the PR8 and Lee strains of the influenza virus in infants from one month to 16 months of age. The close correspondence between the neutralizing antibody levels possessed by mothers and their infants in the previous table and the consistently low level in the age group from one month to 16 months strongly suggest that the concentration of antibodies in the mothers' serum was the factor which determined the antibody concentration in the infants' serum, namely, passive transfer. This is in accordance with the work

of Cohen and Seadron,⁶ who showed that the immune properties of the newborn infant depend upon the immunologic status of the mother. Since the antibodies had not been produced by the child itself, they were soon eliminated, accounting for the low levels in the age group from one month to 16 months.

TABLE II. RESULTS OF NEUTRALIZATION TESTS WITH INFLUENZA A AND B VIRUS AND THE SERA OF INFANTS AGED ONE MONTH TO SIXTEEN MONTHS

NAME	AGE	SERUM ANTIBODY LEVEL	
		PRS TITER	LEE TITER
D. Z.	4 wk.	4	< 2
R. T.	6 wk.	2	< 2
J. V.	2 mo.	2	< 2
C. W.	2 mo.	2	2
J. F.	3½ mo.	< 2	< 2
N. M.	3½ mo.	2	< 2
F. S.	4 mo.	2	< 2
M. S.	4 mo.	< 2	< 2
F. F.	16 mo.	< 2	< 2
Total number		9	9
Average titer		2.6	2

In Table III are presented the figures for the antibody levels in the age group 2 to 7 years inclusive. Here again it will be observed that these levels tend to be low. Of thirty-six children, twenty-eight, or 77 per cent, had a titer of less than 8 to the PRS strain of influenza A virus; eight, or 23 per cent had a titer between 8 and 64, and none had an antibody level of over 64.

Of interest is the fact that the figures of the antibody level against the Lee strain of the influenza type B virus are quite different from those of the PRS strain of influenza type A virus. In the thirty-six children, twenty-seven, or 75 per cent, had a titer of 8 or less to the Lee strain of the influenza type B virus; eight, or 22 per cent, had an antibody level between 8 and 64, and only one had a level over 64. The significance of this will be discussed shortly.

DISCUSSION

The present report presents the results of quantitative tests for neutralizing antibodies against the PRS strain of influenza A virus and the Lee strain of influenza B virus in eighty-one children ranging in ages from one month to 18 years, and in thirteen mothers and their newborn infants.

From the results tabulated, several points of interest were noted. There was a very close correlation between the neutralizing antibody levels possessed by mothers and their infants during the newborn period, which might have been anticipated, for the concentration of antibodies in the maternal serum determines the antibody concentration in the serum of the infant.⁶ As was to be expected, these antibodies disappear rapidly within the first few months of life and from one to 2 years none of these infants possessed protective antibodies.

The antibody level tends to remain low in childhood but after the age of 7 the titers begin to rise. These new antibodies presumably develop in response to exposure and infection by the influenza virus. This is in agreement with the

TABLE III. RESULTS OF NEUTRALIZATION TESTS WITH INFLUENZA A AND B VIRUS AND THE SERA OF CHILDREN FROM TWO TO SEVEN YEARS OF AGE

NAME	AGE (YE.)	SERUM ANTIBODY LEVEL	
		PES TITER	LEE TITER
P. C.	2	< 2	< 2
N. G.	2	2	< 2
S. L.	2	8	16
M. R.	2	< 2	< 2
H. J.	3	< 2	< 2
I. M.	3	< 2	< 2
P. V.	3	< 2	< 2
J. D.	4	2	2
J. F.	4	2	< 2
J. M.	4	2	2
A. P.	4	5.6	2
J. P.	4	2	< 2
S. R.	4	2	< 2
A. W.	4	< 2	< 2
I. K.	4½	2	< 2
K. M.	4½	5.6	< 2
A. R.	4½	2	2
F. T.	4½	< 2	< 2
A. W.	4½	16	< 2
B. C.	5	2.8	2
G. F.	5	8	< 2
R. G.	5	2.5	< 2
E. R.	5	2	2
H. R.	5½	< 2	< 2
L. A.	6	4	2
M. B.	6	5.6	2
S. E.	6	< 2	< 2
A. K.	6	2	2
S. K.	6	2.5	< 2
J. N.	6	22.5	2
M. D.	6	11.2	2
F. B.	6½	2	< 2
S. E.	7	11.2	< 2
B. P.	7	4	< 2
R. S.	7	2.8	4
H. T.	7	2	16
Total number	7	4	< 2
Average titer		36	36
		5.4	3

work of Francis and Magill,² who have shown that between the first and fifth years the serum either protects completely or not at all, suggesting recent infection.

There is an unevenness of immunity to the different strains of the influenza virus, the antibody levels against influenza A virus being consistently higher than against influenza B. According to Rickard and Horsfall,¹ there appear to be two possible explanations for this. The first and most generally offered is that the various antibody levels are the result of previous infection with influenza A virus, which is more prevalent than type B. The second explanation, less likely, though a factor, is the element of maturity which plays a role in the capacity of antibody formation.⁶

There is a large gap ranging from those infants a few months of age, when the antibody levels begin to wane, to the children in the older age group who have acquired some measure of immunity by repeated exposure to and infection with the influenza virus. These children who are most susceptible

TABLE IV. RESULTS OF NEUTRALIZATION TESTS WITH INFLUENZA A AND B VIRUS AND THE SERA OF CHILDREN FROM EIGHT TO EIGHTEEN YEARS OF AGE

NAME	AGE (YR.)	SERUM ANTIBODY LEVEL	
		PR8 TITER	LEE TITER
D. C.	8	2	< 2
B. P.	8	64	11.25
M. S.	8	32	< 2
R. V.	8	5.6	32
S. E.	8½	< 2	2
R. M.	8½	< 2	< 2
J. W.	8½	11.2	< 2
D. C.	9	16	11.2
J. K.	9	8	< 2
J. L.	9	22.5	2
E. P.	9	64	45
E. S.	9	32	< 2
I. W.	9	64	2
M. G.	9½	2.8	< 2
N. F.	10	16	< 2
J. L.	10	2.8	< 2
J. M.	10	16	< 2
L. W.	10	32	< 2
L. Z.	10	22.5	16
I. G.	11½	4	< 2
R. M.	11½	5.6	2.8
P. E.	12	45	22.5
S. G.	12	32	2
I. G.	12	45	16
A. H.	12	64	< 2
M. R.	12	16	< 2
R. S.	12	45	2
I. W.	12	11.25	2.8
T. M.	12½	5.6	< 2
R. P.	13	22.5	< 2
H. S.	13	2	< 2
A. F.	14	128	11.2
O. H.	15	64	2
E. T.	16	32	128
J. G.	17	8	2
A. L.	18	16	< 2
Total number		36	36
Average titer		24	9.7

may benefit from immunization with influenza vaccine, for Salk and co-workers⁵ showed that greater frequency and more severe infections of influenza, as indicated by febrile reactions and duration, were observed among patients with low antibody titers. Furthermore, Adams and co-workers⁷ reported an epidemic of influenza A in infants and children from 3 to 10 years of age with significant immunologic data. They found that serum antibody levels at the onset of illness were low, and during convalescence (two to three weeks after the onset of the disease) rose from thirty-five to forty times over the average pre-infection titers.

A comparison of the incidence of infection at the various antibody levels by Salk had revealed that corresponding antibody titers in control and inoculated individuals appeared to have the same significance as regards probability of contracting influenza. It mattered little whether the antibody titers in inoculated subjects were raised artificially or in uninoculated individuals represented the residual titer of previous clinical exposures.

Thirty-four of the children, or 94 per cent, had a titer of less than 8 to the Lee strain of the influenza B virus and two, or 6 per cent, had a titer between 8 and 64.

In Table IV are presented the antibody levels in the age group 7 to 18 years, inclusive, among thirty-six children. There was a titer of less than 8 to the PRS strain of influenza A virus in ten cases, or 28 per cent. In twenty cases, or 56 per cent, there was an antibody level between 8 and 64, and in six cases, or 16 per cent, the titer was 64 or over.

SUMMARY

1. Quantitative neutralization tests with the PRS strain of influenza A virus and Lee strain of influenza B virus and the serum of mothers and their newborn infants were determined.

2. Similar neutralization tests were also carried out with the sera of infants and children ranging in age from one month to 18 years.

3. It was found that newborn infants possess antibody levels very similar to those of their mothers, and that these antibodies rapidly disappear within the first few months of life. This is in accordance with previous observations, and is evidence that infants possess, by passive transfer from their mothers, antibodies against influenza A and B virus.

4. The antibody levels remain low during early childhood. After the age of 7 they begin to rise, apparently as a result of contact with the virus, and probably represent a specific response to infection.

5. Since the antibody level of sera tends to parallel clinical susceptibility to infection by the influenza virus, there is a very large group of infants and children from several months of age until later childhood where the need for decreasing the susceptibility to influenza by inoculation with influenza vaccine is indicated.

6. There is an unevenness of immunity against the different types of influenza virus; namely, the antibody level for type A is generally higher than that for type B. The explanations for this have been discussed.

7. While the number of cases presented in this report have been small from a statistical point of view, the trend of the results has been in accordance with that reported by others, and is sufficiently consistent to appear significant.

There is a need for further data in regard to antibody levels against the different strains of human influenza virus in the younger age groups, for there is a paucity of such reports in the literature.

The serologic tests were performed by the research laboratories of Parke-Davis and Company, Detroit, Mich.

We wish to acknowledge with pleasure the assistance of Dr. Fred Stimpert, the director of the biological laboratories of Parke-Davis and Company, to Dr. McLean and to Dr. Jonas Salk, whose interest and cooperation aided in the preparation of this paper.

We also wish to acknowledge the assistance of the nurses of the Pediatric clinic of Beth Israel Hospital.

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EFFECT OF INFLUENZA VIRUS VACCINATION IN INFANTS AND CHILDREN, WITH ANTIBODY STUDIES

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IN VIEW of the scant data in the literature on influenza virus vaccination in children, a need for a study of this problem was evident. In the preceding paper,¹ data on the natural incidence of influenza antibodies in children of different age groups was obtained. This established the extremely low titer of antibodies in the age group 6 months to 7 years, a finding in accordance with the observations of others.^{2, 3} These findings seem to indicate the desirability of increasing the low titers in children, particularly in the presence of an anticipated epidemic of influenza.

MATERIALS AND METHODS

The vaccine employed for injection was influenza virus vaccine, type A and B, calcium phosphate adsorbed. In carrying out experiments on the antigenicity in man of calcium phosphate adsorbed influenza virus, Salk⁴ showed that in no instance was the adsorbed virus a less effective antigen: in fact, higher mean antibody titers often developed in subjects given the adsorbed, as compared with a corresponding amount of unadsorbed antigen. Moreover, certain of the data in his experiments suggested the possibility that a smaller amount of antigen adsorbed on calcium phosphate might produce an antibody response similar in degree to that resulting from the use of a relatively larger amount of unadsorbed virus. There were no untoward systemic reactions and no untoward effects as a result of the vaccine in his study.

For measuring the concentration of influenza antibody in the serum, the red cell agglutination inhibition reaction⁵ was employed. The technique was the modification of the U. S. Navy Laboratory Research Unit No. 1 Method.⁶ Tests in the laboratory indicated that if these titers were multiplied by twenty-five they would correspond roughly to those reported by Salk and co-workers⁷ where a correlation between influenza susceptibility and antibody level was found.

The strains of influenza virus employed in these tests were type A, consisting of the PR8 strain, and type B, consisting of the Lee strain grown on chick chorioallantoic fluid.

SUBJECTS

During the months of October, 1946, to March, 1947, a group of 100 children ranging in age from one month to 18 years, was inoculated with influenza virus vaccine type A and B. The dosage of the vaccine was as follows:

$\frac{1}{4}$ c.c. for children up to 3 years of age

$\frac{1}{2}$ c.c. from 3 to 6 years of age

$\frac{1}{2}$ -1 c.c. from 6 to 12 years of age depending on the size of the child

1 c.c. for children over 12 years of age

From the Pediatric Service of Dr. Philip Cohen, Beth Israel Hospital, New York City. This work was aided by a grant from the Loyal League Philanthropies, Inc.

TABLE I

SUSCEPTIBILITY TO INFLUENZA (WEISS STRAIN)	TITER RANGE
Susceptible	< 8
Probably resistant	8-64
Almost certainly immune	> 64

Serum was taken for titration of influenza antibodies before inoculation and again at intervals varying from six days to four months after injection.

Influenza immunization studies by means of determining antibody titers are limited by the fact that pre- and postimmunization samples must be tested at the same time. Because of the uncontrollable day-to-day variations in titer encountered in red cell agglutination inhibition titrations, changes in room temperature, etc., it is necessary that all sera comprising a group be titrated at the same time if over-all comparisons are to be made. Furthermore, since different techniques are used in different laboratories, it is difficult to interpret the actual numerical titers observed in terms of probable protection against influenza. It is standard practice, therefore, to compare pre- and postvaccination sera, because the fold increase in antibody titer is a fairly stable figure, indicating the efficacy of the vaccine regardless of the method of titration, providing the two sera are titrated at the same time.

REACTIONS

In the 100 children inoculated, reactions were mild in the majority of children and consisted of slight soreness at the site of injection. Four had a slight febrile reaction (temperatures of 100° to 100.6° F.) and one child had an elevation of temperature to 102° F. Nodule formation occurred in eight patients and in these the nodules persisted only for a short period of time. There were no systemic reactions in twenty-two patients who were reinoculated, indicating little tendency to sensitization to the influenza vaccine.

Four patients in this study received an unadsorbed influenza A and B vaccine. All of these had slight soreness of the injected arm which persisted for approximately twenty-four hours and one had a mild febrile reaction.

All mothers were questioned regarding a history of allergy in their children, particularly egg allergy, for the influenza virus is cultivated in chick embryo allantoic sac and obtained from the allantoic fluid. This is important, for if influenza vaccine is administered to egg-sensitive individuals, severe allergic reactions may ensue. We inoculated allergic children without untoward reaction, but did not inoculate any known egg-sensitive child. Ratner and Untracht,⁸ in a group comprising 108 highly allergic children who were studied completely for their allergy, found that approximately 10 per cent were sensitive to egg-white protein. However, only 4.6 per cent were sensitive enough to be potential hazards for influenza vaccine administration.

Only 0.5 per cent of the general population are hypersensitive to egg, hence the use of influenza vaccine is not harmful to 99.5 per cent, which includes all the allergic persons who are sensitive to proteins other than egg. However, Ratner and Untracht advise that all persons should be tested intradermally

with undiluted vaccine, using 0.02 c.c. before administering every dose because a history of egg sensitivity is not as reliable as an intradermal test. Furthermore, an occasional child may not have an apparent clinical history of egg sensitivity and yet by skin testing with egg protein (and testing with influenza vaccine) may be shown to be extremely sensitive to egg.

Curphey⁹ reported a case in which a fatal reaction occurred following an injection of influenza vaccine. Although the implication was made that exitus was due to extreme sensitivity to egg antigen contained in the vaccine, it appears to us more likely that the reaction was of a more complex biological nature akin to the Schwartzman phenomenon.

Table II presents a summary of the results of complete sets of pre- and postvaccination sera from forty children who received influenza vaccine types A and B calcium phosphate adsorbed.

TABLE II. SUMMARY OF THE RESULTS OF COMPLETE SETS OF PRE- AND POSTVACCINATION SERA FROM FORTY CHILDREN WHO RECEIVED ONE INJECTION OF INFLUENZA VACCINE TYPES A AND B. CALCIUM ADSORBED

NAME	AGE	PREVACCINATION TITER		POSTVACCINATION TITER		INTERVAL (DAYS)	CHANGE IN PRE TITER	CHANGE IN LEE TITER
		PRE	LEE	PRE	LEE			
R. T.	6 wk.	2	< 2	2	< 2	21	< 2X	< 2X
J. V.	2 mo.	2	< 2	2	< 2	30	< 2X	< 2X
C. W.	2 mo.	2	< 2	2	< 2	6	< 2X	< 2X
N. M.	3½ mo.	2	< 2	2	< 2	21	< 2X	< 2X
P. C.	1½ yr.	< 2	< 2	2	< 2	14	< 2X	< 2X
M. R.	2 yr.	< 2	< 2	11.2	5.6	14	8X	4X
I. M.	3 yr.	< 2	< 2	11.2	5.6	51	8X	4X
S. R.	4 yr.	< 2	< 2	5.6	2	34	4X	< 2X
J. F.	4 yr.	2	< 2	2	45	31	< 2X	32X
J. P.	4 yr.	2.8	< 2	90	64	76	32X	45X
A. P.	4 yr.	2	< 2	4	< 2	28	2X	< 2X
K. M.	4½ yr.	2	< 2	11.2	32	28	5.6X	16X
G. F.	5 yr.	22.5	< 2	256	90	48	11.4X	50X
H. R.	5½ yr.	4	2	180	2	44	45X	< 2X
S. E.	6 yr.	< 2	2	22.5	32	15	16X	16X
A. K.	6 yr.	22.5	< 2	180	180	34	8X	128X
L. A.	6 yr.	5.6	< 2	256	45	14	45X	32X
M. D.	6½ yr.	2	< 2	2	45	35	< 2X	32X
R. S.	7 yr.	2	16	2.8	180	42	< 2X	11.2X
B. P.	7 yr.	2.8	4	90	16	76	32X	4X
S. E.	7½ yr.	4	< 2	45	22.5	17	11.2X	16X
M. S.	8 yr.	32	< 2	64	32	35	< 2X	22.5X
J. G.	8 yr.	2	< 2	11.2	4	17	5.6X	2.8X
S. E.	8½ yr.	< 2	2	90	> 256	42	50X	256X
R. M.	8½ yr.	< 2	< 2	4	8	28	2.8X	5.6X
J. K.	9 yr.	8	< 2	256	32	34	32X	22.5X
R. L.	9 yr.	22.5	< 2	90	8	42	4X	4X
E. S.	9 yr.	32	< 2	64	16	33	2X	9X
M. G.	9½ yr.	2.8	< 2	64	4	28	22.5X	2.8X
J. M.	10 yr.	16	< 2	180	< 2	31	11.2X	< 2X
L. W.	10 yr.	32	< 2	256	128	14	8X	90X
L. Z.	10 yr.	22.5	16	360	45	14	16X	2.8X
R. M.	11½ yr.	5.6	2.8	90	45	35	16X	16X
I. W.	12 yr.	11.5	2.8	128	180	18	11.2X	64X
S. G.	12 yr.	32	2	108	32	32	4X	16X
R. S.	12 yr.	45	2	64	45	14	< 2X	22.5X
P. E.	12 yr.	45	22.5	128	45	41	< 2.8X	2X
M. R.	12 yr.	16	< 2	11.2	< 2	26	< 2X	< 2X
I. G.	12 yr.	45	16	128	32	28	2.8X	2X
H. S.	13 yr.	2	< 2	300	256	28	180X	180X

There were eighteen patients ranging in age from 6 weeks to 7 years. In this group, sixteen (88 per cent) had an antibody level against the PR8 strain of influenza virus below 8, and two (12 per cent) had a titer of 22.5. After inoculation with influenza vaccine nine (50 per cent) had a titer below 8, four (22 per cent) had a level between 8 and 64, and five (28 per cent) had a level over 64.

In this age group the prevaccination antibody levels against the Lee strain of influenza B virus were as follows: eighteen (100 per cent) had a level below 8. Following injection with the vaccine, ten (55 per cent) had a level below 8, six (34 per cent) had a level between 8 and 64, and two (11 per cent) had a level over 64.

There were twenty-two patients varying in age from 7½ years to 13 years, inclusive. The prevaccination antibody titers against the PR8 strain of influenza A virus gave the following results: Ten (45 per cent) had a level of 8 or below, twelve (55 per cent) had a titer between 8 and 64, and no cases had a level over 64.

Following inoculation with influenza vaccine, two (9 per cent) had a level against the PR8 strain below 8, three (14 per cent) had a level between 8 and 64, and seventeen (77 per cent) had a titer of 64 or over.

The prevaccination antibody levels against the Lee strain of influenza B virus in this group revealed the following: eighteen (82 per cent) had a titer below 8, and four (18 per cent) had a level between 8 and 64.

The figures for the antibody levels against the Lee strain of type 8 influenza virus after injection with the vaccine showed: four (18 per cent) had a level below 8, thirteen (59 per cent) had a titer between 8 and 64, and five (23 per cent) had a level over 64.

Reviewing the above data, we find that in the group up to the age of 7 years there was a significant increase in antibody titers in a large percentage of cases. For example, in those cases whose antibody levels against the PR8 strain were below 8, the prevaccination percentage fell from 88 to 50 per cent after vaccination, indicating decreased susceptibility, and against the Lee strain prevaccination susceptibility fell from 100 to 55 per cent. On the other hand, the percentage of cases whose levels against the PR8 strain were over 64 rose from zero before injection to 28 per cent after injection, indicating probable immunity. The percentage of cases with antibody levels over 64 against the Lee strain was zero before inoculation and 11 per cent after inoculation.

Even more impressive are the percentages in the age group over 7 years. Whereas 45 per cent of the children had a prevaccination titer below 8 against the PR8 strain, the figure fell to 9 per cent after injection with the vaccine. On the other hand, the percentage of children with a titer of 64 or over rose from zero before inoculation to 77 per cent following injection.

Eighty-two per cent of the cases had prevaccination antibody levels below 8 against the Lee strain of influenza B virus and the figure fell to 18 per cent after injection.

There were no children who had a titer over 64 against the Lee strain before injection whereas 23 per cent had levels above this figure after inoculation.

Table III presents a summary of the fold increase in antibody titers after inoculation with influenza type A and B vaccine according to age groups. It is noted that the response of infants less than 2 years of age to the vaccine is poor, the fold increase in mean titer being less than twice to both the PR8 and Lee strain.

In the age group from 2 to 7 years, the response to inoculation is marked, the increase in mean titer against the PR8 strain rising 8.5 times and to the Lee strain 23.3 times.

In older children, the rise in antibody titer after inoculation is equally sharp. From 7 to 10 years the fold increase against the PR8 strain of influenza type A virus was seven times and against the Lee strain of influenza type B virus was ten and one-half times. The respective figures in the age group 10 to 13 years were eight and one-half times and twelve times.

Although the mean antibody response to injection in children over 2 years of age was on the whole very satisfactory, comparable to adults, there was an unevenness of this response as some children did not produce antibody against the PR8 strain and others failed to produce a satisfactory increase in antibody against the Lee strain.

TABLE III. SUMMARY OF THE FOLD INCREASE IN ANTIBODY TITERS AFTER INOCULATION WITH INFLUENZA TYPE A AND B VACCINE ACCORDING TO AGE GROUPS

AGE (YR.)	NO. CASES	RESPONSE TO	
		PR8	LEE
Less than 2	5	< 2X	< 2X
2-7	13	8.5X	23.3X
7-10	11	7X	10.5X
10-13	11	8.5X	12X

Because of the observed findings that in some children, particularly the younger, the increase in antibody levels was inadequate, a second injection of influenza vaccine was given to twenty-two patients, from which complete serologic data was obtained in five. These results are tabulated in Table IV. Although the number of cases is small, nevertheless, our findings are in accord with those of others,^{11, 12} namely, that there may be a lack of response to a second injection of influenza vaccine in older children. It seems likely that the first injection acts as a booster dose, especially in older children and adults, because they have already had repeated exposures to infection by the virus. The second injection, therefore, given within a relatively short interval, would not be antigenically stimulating. In young children it is possible that two injections may be needed, since our data and observations by others have revealed a low natural incidence of circulating antibody in younger age groups; therefore, a single dose may not suffice as a booster. This matter is of some importance and is being further studied.

Francis and Salk^{11, 12} reported similar observations in a group of sixteen individuals. These authors postulated that failure of the second inoculations (given four months after the first) to provoke a further rise in antibody titer in many of the subjects and only a slight rise in others might be due in part to combination of antigen with antibody rendering the virus antigenically ineffective.

CLINICAL DATA

The epidemic of influenza which was anticipated during the fall and winter months of 1946-1947 did not fully materialize, although there was a delayed outbreak in March, 1947,* therefore, the number of children studied is far below expectancy. As stated previously, 100 patients were inoculated with influenza virus type A and B. Of these, seventy-eight received one injection and twenty-two received a second injection at varying intervals from two weeks to three months after the first inoculation. These 100 children were compared with a group of 200 controls of the same age groups who received no vaccine.

Fully realizing the difficulty of making a diagnosis of influenza without confirmatory virus studies, we used the following clinical and laboratory data for the diagnosis of influenza: A respiratory infection with fever, cough, low white blood count, headache, generalized body aches, slight irritation of the throat, and mild nasal congestion. No children with a tonsillar exudate were included in the study. On physical examination there were found as a rule a flushed skin, some redness of the nasal and pharyngeal mucosa, and a paucity of findings in the lungs on auscultation and percussion.

Using the above criteria, we found three cases (3 per cent) of influenza in the 100 children who were inoculated and nineteen cases (9.5 per cent) in the 200 controls. Although the percentage of cases in the latter is over threefold that of the inoculated children, we feel that the significance of this is far from established in view of the absence of the study during a widespread epidemic involving a larger group of cases. Hirst and associates,¹³ in an investigation of the occurrence of epidemic influenza A in seven widely separated populations

TABLE IV. SUMMARY OF RESULTS ON COMPLETE SETS OF PRE- AND POSTVACCINATION SERA FROM PATIENTS RECEIVING A SECOND INJECTION OF CALCIUM PHOSPHATE—ADSORBED INFLUENZA VACCINE

NAME	AGE	PREVACCINATION TITER		POSTVACCINATION TITER		INTERVAL (DAYS)	CHANGE IN PRS TITER	CHANGE IN LEE TITER
		PRS	LEE	PRS	LEE			
J. F.	4 yr.	2	< 2	2	45	31	< 2X	32X
J. F. (Second bleeding)						67	< 2X	11.2X
M. D.	6½ yr.	2	< 2	2	45	35	< 2X	32X
M. D. (Second bleeding)						113	2X	45X
R. M.	8½ yr.	< 2	< 2	4	8	28	2.8X	5.6X
R. M. (Second bleeding)						93	8X	11.2X
J. M.	10 yr.	16	< 2	180	< 2	31	11.2X	< 2X
J. M. (Second bleeding)						49	11.2X	< 2X
S. G.	12 yr.	32	2	128	32	32	4X	16X
S. G. (Second bleeding)						56	4X	16X

*Salk, J. E.: To be published (Am. J. Pub. Health).

one year after vaccination of part of these groups with PR8 strain of influenza virus A and Lee strain of influenza virus B, showed that the attack rate among vaccinated persons was consistently lower than that of control individuals. The average reduction in the attack rate was approximately 35 per cent. Furthermore, evidence¹⁴ on the effect of vaccination with influenza virus showed that the incidence of epidemic influenza was reduced by about 75 per cent when the period between injection and epidemic was short.

DISCUSSION

The present report covers a group of children varying in age from one month to 18 years. In the age groups over 2 years, the results seemed significant, for serologic evidence indicated that the inoculated children had from seven to twenty-three times as much circulating antibody after injection as they had previously.

The vaccinated children showed a reduction in the attack rate during a period up to five months from the onset of vaccination. These results compare favorably with observations recorded by others.^{13, 15}

Two of the three cases of influenza in the inoculated group occurred three months after inoculation and one occurred seven weeks after injection. Most of the evidence in the report of members of the Commission on Influenza covered cases infected up to approximately two months after injection. It was found in those studies that the effect of inoculation was greatest in the second week following injection (about 85 per cent reduction) and was lowest in the sixth and seventh weeks when the reduction due to injection fell to approximately 40 per cent.

It is probable that the attack rate is lower if the interval between inoculation and infection is shorter. However, in view of the fact that the anticipated epidemic in the fall and winter of 1946-1947 did not become manifest, the number of cases was far below expectancy, and while our vaccinated group had a lower incidence, further studies are needed before definite conclusions of the clinical efficacy in children can be drawn.

If the degree and duration of immunity are reflected in the level to which antibody titer is raised and maintained, then it may be stated that although the effect of vaccination is highest in the first six weeks, some protection in the majority of cases may persist for as long as a year.^{13, 16} Nevertheless, information at present indicates the desirability of re-immunization in the fall of the year, at which time a higher risk of exposure is anticipated.

Hirst¹³ states that there would be much greater economy in the administration of influenza vaccine if it were to be given in the face of an outbreak after its identification, rather than if the vaccine were administered in advance of each epidemic season, since the exact seasonal onset and yearly periodicity of influenza epidemics is too capricious to permit accurate prediction. Salk,¹⁷ on the other hand, feels that it is impractical to await the onset of the epidemic before using the vaccine. The speed with which influenza spreads is too great to attempt to stop it by vaccination. About a week is required for the immunization effect to become apparent, while the incubation period of influenza is less

than two days. Thus it would be futile to vaccinate those who had been in contact with a case in order to prevent the disease; furthermore, the vaccine is not effective therapeutically.

SUMMARY

1. From October, 1946, to March, 1947, 100 children ranging in ages from one month to 18 years were inoculated with influenza virus type A and B vaccine adsorbed on calcium phosphate. The dosages given to the different age groups have been outlined.

2. Reactions were mild and consisted of slight local soreness for twenty-four hours in the majority of cases. Four children had a slight febrile reaction (100° to 100.6° F.), and one child had an elevation of temperature to 102° F. Nodules following injection appeared in eight cases and persisted for a short time only.

3. Of the 100 children inoculated, complete serologic data including pre- and postvaccination antibody titers were obtained in forty children.

4. Of these forty children, twenty-two received a second injection of the vaccine, at intervals from two weeks to three months. Complete serologic data was obtained in five children following the second inoculation. There were no systemic reactions to the second injection of the vaccine. In our study there were no cases of induced sensitivity to the calcium phosphate-adsorbed vaccine in those children who received more than one injection.

5. Two hundred children of similar ages as the vaccinated children served as controls. In the injected children there were three cases of influenza, an attack rate of 3 per cent and in the controls there were nineteen cases, an attack rate of 9.5 per cent.

6. There was a significant response to vaccination in children over 2 years of age, as judged by antibody levels, for serologic evidence indicated that the injected children had a rise in titer from seven to twenty-three times.

7. Although the average antibody response to injection in children over 2 years of age was, on the whole, very satisfactory, and comparable to adults, there was an unevenness of this response as some children did not produce antibody against the PR8 strain and others failed to produce a satisfactory increase in antibody against the Lee strain.

8. It is probably significant that children below 2 years of age did not respond to the vaccine with good antibody production.

9. It was observed that the second inoculation did not produce a further sharp rise in circulating antibody in children over 2 years of age.

10. The results of our studies are in agreement with the data and observations of other investigators; namely, that subcutaneous vaccination with a vaccine containing inactivated influenza virus, types A and B, adsorbed on calcium phosphate is usually followed by a satisfactory rise in circulating antibody against these viruses in children over 2 years of age.

11. In view of the fact that a widespread epidemic of influenza anticipated during the fall and winter of 1946-1947 did not fully materialize, the number of cases of influenza was far below expectancy. Although our vaccinated group had a reduction in the attack rate, further studies are needed to prove conclu-

sively the clinical efficacy of influenza vaccination in children, and no final conclusion regarding the protective effect of influenza vaccination in children can be drawn from this study.

The serologic tests were performed by the research laboratories of Parke-Davis and Company, Detroit, Mich.

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overheight is characteristic of juvenile diabetes at the outset, a certain number of diabetic children become stunted."

The height of each of the diabetics in the present study was taken at the time of his first visit to the hospital. Since these children were first admitted at varying lengths of time after the onset of the disease, measurements of height near onset were not available in all instances. It was felt that any measurement of height taken within three months of onset would be representative of the child's stature rank at onset. Ninety-two of the children were found to have been admitted and first measured within three months after acquiring diabetes. The measurement on each of these children was referred to a standard chart* for the purpose of determining its relation to the height distribution of normal children.

The heights of the children first examined six months or more after onset were also referred to the normal chart in an effort to determine the association between stature and delay of treatment. It was found that inclusion in this group of those children first admitted three years or more after acquiring the disease gave the group a disproportionately high deviation from normal. Therefore, a third category was established to contain those children first examined at Children's Hospital three years or more after onset of the diabetes.

For each of these three groups the frequencies of admission heights falling in each quarter of the normal range were determined. The results are shown in Table I.

TABLE I

POSITION IN NORMAL DISTRIBUTION	LENGTH OF DELAY FROM ONSET TO ADMISSION					
	0 TO 3 MONTHS		6 MONTHS TO 3 YEARS		OVER 3 YEARS	
	NO.	%	NO.	%	NO.	%
Above Q_2	22	24	9	14	1	4
Q_2 to Q_3	21	23	15	23	3	10
Q_3 to Q_4	17	18	17	27	7	24
Below Q_4	32	35	23	36	18	62

Each of these "per cent" columns was compared with the "normal" frequencies of 25 per cent in each quarter of the height distribution. The Chi-square procedure was used. The objective was to determine whether or not the diabetic child at the time of onset differed significantly from a normal child.

It was found that for the subjects measured within three months of onset, Chi^2 equals 5.8, which for three degrees of freedom is not statistically significant. It may be inferred, then, that these diabetic subjects were no different in height from normal children, that is, at the age of onset they showed no tendency to be either taller or shorter than normal children.

The Chi^2 for the subjects who were admitted six months to three years after onset was 9.8, which is significant at the 2 per cent level of confidence. Inspection of the frequency tabulation indicates a markedly high frequency in the lower

*Growth charts prepared by the Iowa Child Welfare Research Station, State University of Iowa, were used. These norms were derived from children attending the University of Iowa Experimental Schools, 1930-1945. The children were of a higher socioeconomic status than the diabetic children but were similar in ethnic stock, secular period, and geographic location. The portions of these charts extending from 5 to 18 years of age have been published in the *American Journal of Public Health*, 36: 1365-86, 1946.

quarter and a low frequency in the upper quarter. The systematic difference is even more striking for the subjects who were first admitted three years or more after onset. The Chi^2 for this group was 82.2, which is significant at the 1 per cent confidence level.

The above method of analysis has considered the height at onset from the standpoint of *direction*, rather than magnitude of differences. It was next thought pertinent to obtain figures representing the *amount* of deviation from normal height. For this purpose, the admission stature of each of the subjects was compared with the mean normal height for his age. The children in each of the "lapse between onset and treatment" categories were subdivided into three subgroups on the basis of "age at onset." For each subgroup, the mean absolute difference from normal in inches was determined (see Table II).

TABLE II

LAPSE FROM ONSET TO TREATMENT	AGE AT ONSET							
	0-5 YEARS		6-9 YEARS		10-16 YEARS		17-20 YEARS	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
0-3 months	32	-0.07	22	-0.04	38	-0.50	92	-0.24
6 months-3 years	10	-1.41	18	-1.28	36	-0.95	64	-1.11
Over 3 years	1	-*	8	-2.21	20	-4.61	29	-3.92

*Because of the presence of only one child in this subgroup, no deviation is given.

The patients who were admitted within three months of onset of diabetes mellitus differed from the normal by an average of -0.07 inches at ages 0 to 5 years, -0.04 inches at 6 to 9 years, -0.50 inches at 10 to 16 years, and by -0.24 inches for all ages together. In view of the Chi^2 findings reported above, these differences are probably not significant. Even if a slight difference were assumed, this would appear to be no greater than would be expected as a result of the lower socioeconomic status of the diabetic children. Again, this study lends no credence to the position that the height of diabetic children at the time of onset of diabetes is either greater or less than that of normal children.

The deviation for those children admitted six months to three years after onset shows marked retardation, and that for those first measured three years or more after onset shows still more extreme retardation.

Weight at Onset.—The weight of each child was obtained and recorded at the time of his first admission to the hospital. One of the symptoms characterizing the onset of diabetes mellitus in the child is a loss of weight frequently so noticeable as to be the factor which motivates the parents to bring the child to the hospital for the first time. Because of this, the weight of the child at the time of onset could not be considered indicative of his weight rank prior to the onset of diabetes. It was expected that the weight taken within three months of onset might deviate markedly from normal.

For the purpose of comparing the distribution of weights near onset with the distribution of weights of normal children, each of the diabetic weights was referred to the normal growth charts, and its position in relation to the median was determined. Of the ninety-two children who were admitted to the hospital within three months of the onset of diabetes, only ten children, or 11 per cent,

fell above the median, and the remaining 89 per cent fell below the median normal weight for their age.

The weight of each child in this group was compared with the normal median weight for a child of his age, and the absolute amount of difference was determined. The group was subdivided into three smaller groups on the basis of age of onset, and the mean absolute differences for each subgroup, and the group as a whole, were calculated. The results in kilograms appear in Table III.

Since these children were found to be of normal height for their ages, these means represent very significant deviations from their normal weights.

TABLE III

LAPSE FROM ONSET TO TREATMENT	0-5 YEARS		6-9 YEARS		10-16 YEARS		0-16 YEARS	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
0-3 months	32	-1.49	22	-2.67	38	-7.38	92	-4.20

HEIGHT AND WEIGHT GAIN OF DIABETIC CHILDREN 5 TO 9 YEARS OF AGE UNDER PEDIATRIC TREATMENT

The second aim of the present study was to reveal any true difference between the diabetic children and normal children in rate of gain in height and weight. More specifically, an attempt was made to discover whether or not the height and weight gains of children between 5 and 9 years of age under treatment for diabetes mellitus are different from those for normal children.

Comparisons were made using annual increment values for height and weight representing each group. The method of obtaining these values was the same in both instances. For the diabetic group, there were twenty subjects with growth records spanning the age period 5 to 7 years, and sixteen with records extending between ages 7 and 9 years. These records were plotted on graphs, and the annual increment typifying each biennial period determined by finding the total gain for each two-year period and halving it. Constituting the normal group, there were fifty-five children with records covering the age interval 5 to 9 years. For each of these fifty-five children, growth curves were plotted and annual increments obtained typifying the two biennial periods 5 to 7 years and 7 to 9 years. The normal children were Iowa City residents in attendance at the University of Iowa experimental schools. While they represented a higher socioeconomic level than the diabetic children, it was felt that the two groups were well equated from the standpoint of adequate diet, the diabetic group having had the advantage of sustained pediatric advice regarding dietary.

Findings for Height.—The results of the comparison of the two groups for height in inches are shown in Table IV.

TABLE IV

AGE	DIABETIC		NORMAL		DIFFERENCE IN GAIN	SIGNIFICANCE	
	NO.	MEAN GAIN PER ANNUM	NO.	MEAN GAIN PER ANNUM		t VALUE	CONFIDENCE LEVEL
5-7	20	2.35	55	2.63	0.38	4.8	1%
7-9	16	1.91	55	2.22	0.31	3.7	1%

The increments for the diabetic children are found to be significantly lower than those for the normal group.

Because the original hypothesis was that diabetic children under pediatric treatment would not differ significantly in rate of growth from normal children, variables known to be related to the rate of growth of diabetic children were studied.

It has been shown that (a) diabetic subjects who begin treatment within a relatively short period of time after the onset of diabetes do not differ significantly in height at admission from normal children of their age, and (b) diabetic subjects who do not begin treatment for several months after the onset of diabetes show some retardation in height. It seemed reasonable that some degree of association might exist between the duration of the disease prior to the initiation of therapy, and the rate of growth after treatment began. After eliminating from each age group all those first admitted six months or more after the onset of diabetes, the mean increment was found to be identical with that of the total group for the period 5 to 7 years, and practically identical (.06 in above) for the period 7 to 9 years. It follows that this factor is not responsible for the lower than normal mean increments of the diabetic children.

The subjects were divided according to the length of period of treatment prior to the increment being studied. To keep as many factors as possible under control, only those were included who were admitted less than twelve months after the onset of diabetes. It was found that of these, eight from the two age groups combined had been under treatment less than one year prior to the increment being studied. Three of these were girls, and five were boys. This group was found to have a mean increment not differing significantly from the normal mean annual increment from 5 to 9 years. The mean increment for those being studied more than one year after therapy began was significantly lower than the normal. These findings are shown in Table V.

TABLE V

AGE	N	DIABETIC MEAN	NORMAL MEAN	DIFFER- ENCE	SIGNIFICANCE	
					t	CONFIDENCE LEVEL
Those for whom increment began less than 1 year after treatment	5-7 } 7-9 }	8	2.96	2.43	0.17	1.7
Those for whom increment began more than 1 year after treatment	5-7 } 7-9 }	21	2.11	2.43	0.32	4.6
						1%

The second group was composed of fifteen boys and six girls.

Though the increments both differ from the normal in the same direction, the statistical insignificance of the first would indicate that the children grow more nearly normally during the first year of treatment than during subsequent years. It was found that the largest increments during the first year of treatment were attained by those children who were most retarded in height when treatment began. The number of cases is small, and the relationship is not per-

fect, but the findings suggests that the organism tends to attempt compensation for retardation during the first year of treatment.

Summarizing the foregoing observations, it is evident that the mean annual increment for these thirty-six children between the ages of 5 and 9 was lower than that for the control group. No association was found between the size of the increment and the duration of treatment, the increment being larger during the first year of therapy than during subsequent years, especially if the child was in the lower quarter of the height range when admitted.

Findings for Weight.—The mean annual increments in weight for the two age periods were compared with the mean annual increments for the fifty-five normal children. The results in pounds are as follows:

TABLE VI

AGE PERIOD	DIABETIC MEAN	NORMAL MEAN	DIFFERENCE	SIGNIFICANCE
5-7	5.47 lb.	6.00 lb.	0.53	$t = 1.0$
7-9	5.41	6.75	1.34	$t = 2.4$

The difference between the diabetic increment and the normal increment is not statistically significant for the period 5 to 7 years. For the period 7 to 9 years the difference is significant at the 2 per cent level of confidence. Though the differences for the first group is not significant, the differences for both groups indicate a slightly less than normal gain for the diabetic children.

The difference in height was found to be significant for each age period, the diabetic children gaining slightly less in stature than normal children. The proportionately higher gains in weight than in height for the 5- to 7-year period might reflect the fact that the children were underweight when admitted and that at this lower age level, more were still regaining normal weight for their height. This is borne out by the finding that the mean increment for those children under treatment less than one year before the increment being studied, exceeded the normal by .39 lb.

ADULT HEIGHT STATUS OF SUBJECTS HAVING DIABETES MELLITUS DURING CHILDHOOD

The third specific aim of the present study was to compare the adult height of the diabetic subjects with the adult height of normal subjects. On the basis of findings for normal subjects, it was initially assumed that for boys, any measurement of height recorded after 17 years of age, and for girls, any measurement recorded after 16 years, would be approximately equal to ultimate adult height. Examination of the records revealed, however, that an extraordinarily large number of diabetic boys made significant gains in height after 17 years of age, and that likewise, an unusually large number of girls made gains after

TABLE VII

SEX	NO.	MEAN DEVIATION FROM NORMAL; AGE 17 (BOYS); AGE 16 (GIRLS)	MEAN GAIN AFTER 17 (BOYS); AFTER 16 (GIRLS)	ULTIMATE MEAN DEVIATION FROM NORMAL
Males	21	-1.89	1.74	-0.13
Females	24	-0.54	0.61	+0.08

16 years. To determine the extent of this gain and its effect upon the ultimate adult height of the diabetic subjects, the amount of gain for each was determined, and the mean gain for each sex was calculated. It was found that there was a total of twenty-one boys for whom heights were recorded (a) at 17 years, and (b) at one or more subsequent ages. For girls, a total of twenty-four had heights recorded at age 16 and at one or more subsequent ages. The final height records were at ages varying from 18 years for boys and 17.5 years for girls, to 28 years. The mean gain in height after 17 years of age for the twenty-one boys was 1.7 inches, and after 16 years for the twenty-four girls, was 0.6 inches.

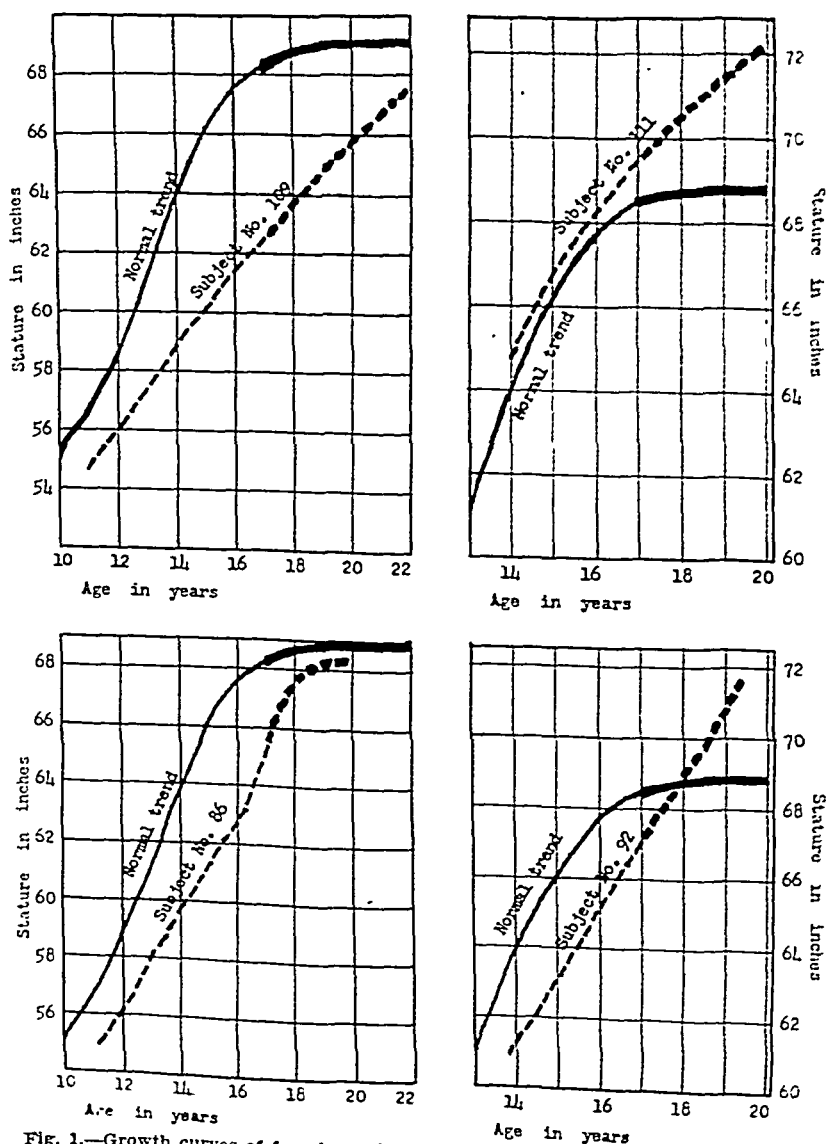


Fig. 1.—Growth curves of four boys showing gains in height after 17 years of age.

The height of each diabetic boy at age 17 years was compared with the 17-year mean for normal boys. Similarly, the height of each diabetic girl at 16 was compared with the normal mean for girls at 16. The absolute amounts of deviation in inches were recorded and the mean deviation for each sex was calculated. Likewise, the absolute deviation from normal of the final recorded height for each subject was determined, and the average deviation of each sex was calculated.

The results in inches are shown in Table VII.

These results indicate that though the diabetic boys are, on the average, 1.9 inches shorter than the normal at 17 years of age, they gain an average of 1.7 inches after 17, making their ultimate height practically equal to the normal height for adult males.

The average amount of growth expected after 17 years of age for the normal male is less than 0.5 inch. Of the twenty-one subjects studied, all but two showed some gain in height. Twelve boys, or 57 per cent, gained an amount in excess of 1 inch. Nine boys, or 43 per cent, gained an amount in excess of 2 inches; and two boys, subjects 92 and 109, gained 4.0 and 4.3 inches respectively. These latter two growth curves and two others characteristic of those showing gains after 17 years were plotted against the normal curve, and are presented in Fig. 1. It will be seen that for each subject, growth continued beyond the normal age for termination of growth, and that, with the exception of No. 86, the curves were still accelerated at the time of the final recorded height.

The findings for girls indicate a similar trend. Though the diabetic girls were, on the average, .54 inch shorter than the normal at 16 years of age, they gained an average of .61 inch after 16, making them practically normal in adult stature. The average amount of gain expected for girls after 16 years of age is less than 0.2 inch. Of the twenty-four diabetic girls studied, four girls, or 17 per cent, gained more than 1 inch, and two girls, or 8 per cent, gained more than 2 inches.

These findings indicate that although those diabetic subjects tended to be abnormally short at the usual age of growth termination, additional growth in height occurred, resulting in a normal mean adult stature for the group.

SUMMARY AND CONCLUSIONS

Utilizing data for height and weight, the body size and growth rates of 200 white children under treatment for diabetes mellitus are compared with the body size and growth rates of normal children. The data for both groups were collected in Iowa between 1928 and 1945.

Ninety-two children first measured within three months of the onset of diabetes mellitus had an average height essentially the same as that for normal children. In other words, it was found that children who acquire diabetes mellitus are of normal height for age at the time of onset of the disease.

The heights of children who were first examined between six months and three years after the onset of diabetes mellitus differed from normal height for age by an average of -1.1 inches; of children first examined more than three

years after onset, by an average of -3.9 inches. These findings demonstrate a clear relationship between height and the duration of untreated or inadequately treated diabetes.

The children first examined within three months of the onset of diabetes weighed, on the average, 4.2 kg. less than the normal weight for their height. These findings for initial height and initial weight demonstrate the necessity for prompt treatment of diabetes mellitus.

The mean annual increment in height between age 5 and age 7 was found to be significantly lower for diabetic children than for normal children. The magnitude of the difference was 0.4 inch. Similarly, the mean annual increment between age 7 and age 9 was found to be 0.3 inch lower for diabetic children than for normal children.

No relationship was found between the size of increment and the time between onset and treatment. It was found that the increment during the first year of treatment was more nearly normal than subsequent increments, especially if the child was in the lower quarter of the height distribution when first examined. This finding suggests that the organism tends partially to compensate for any previous retardation during the first year of therapy.

The mean annual gain in weight for diabetics between the ages of 5 and 7 was found to be slightly, though not appreciably, less than the gain for normal children. The mean annual gain between 7 and 9 years was substantially less for the diabetic children than for normal children.

The diabetic boys were, on the average, 1.9 inches shorter than normal boys at 17 years of age. However, later than normal growth in height enabled them to achieve an average gain of 1.7 inches after 17 years of age. As a result of this gain, their mean adult height was essentially the same as normal adult height. The diabetic girls deviated from normal by an average of 0.5 inch at 16 years of age, and gained an average of 0.6 inch after 16 years.

These gains greatly exceed those expected after 17 years of age for the normal boy, or after 16 years of age for the normal girl. Although both sexes were, on the average, shorter than the normal height at the time that growth is usually terminated for the normal child, additional gains led to the attainment of normal adult stature.

The author wishes to express her appreciation to Drs. Howard V. Meredith and Julian D. Boyd for their valuable guidance during the progress of this study.

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FURTHER STUDIES OF NITROGEN AND FAT METABOLISM IN INFANTS AND CHILDREN WITH FIBROSIS OF THE PANCREAS

ALFRED T. SHOHL, M.D.†

STUDIES of fat and nitrogen metabolism in pancreatic insufficiency in infants and children were initiated by Shohl, May, and Shwachman and their first results were reported in 1943.¹ The objectives then stated were to gather information concerning the aberrations of metabolism in this group of patients, to provide an additional basis for early diagnosis and differentiation from other

PERIOD NO.	PATIENT, AGE	WEIGHT (KG.)	DATE, DAYS IN PERIOD	TYPE OF DIET	INTAKE PER DAY				FM (GM.)
					CALORIES PER KG.	NITROGEN			
						(GM.)	(GM. PER KG.)		
1.	M. E. H. 4½ yr.	12	10/5/42- 10/14/42 9 days	Whole cow's milk, high carbohydrate	75	3.25	0.27	23.5	
2.	M. E. H. 4½ yr.	12	10/26/42- 10/29/42 3 days	Whole cow's milk, high carbohydrate, sulfadiazine	70	5.85	0.49	32.4	
3.	B. H. 5¾ yr.	14	5/2/45- 5/5/45 3 days	Whole cow's milk, high carbohydrate, sulfadiazine	112	7.41	0.53	49	
4.	M. C. 22 mo.	10	3/24/44- 3/26/44 2 days	Whole cow's milk, hospital diet, sulfadiazine	64 (Milk only)	4.81	0.48	38	
5.	V. S. 9 mo.	4.4	10/14/42- 10/17/42 3 days	Evaporated milk formula	114	2.22	0.51	19	
6.	V. S. 9 mo.	4.4	11/3/42- 11/6/42 3 days	Evaporated milk formula	228	4.44	1.0	39	
7.	E. M. 3¼ yr.	10	10/12/43- 10/15/43 3 days	Fat-free milk, low fat solids, sulfadiazine	81	6.0	0.6	5	
8.	E. M. 3¼ yr.	10	10/15/43- 10/18/43 3 days	Fat-free milk, low fat solids, sulfadiazine	91	6.51	0.65	5.	
9.	E. M. 3½ yr.	10	11/12/43- 11/16/43 4 days	Fat-free milk, low fat solids	93	6.09	0.61	5.	

*Mead, Johnson and Company.

†Parke Davis Co.'s Enteric Granules, three times U.S.P. potency.

‡Prepared by Mead, Johnson and Company; composed of casein hydrolysate (Amigen) 20 per cent, dextrimaltose 73.3 per cent, salts 6.7 per cent, but no fat

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospital, Boston. Compiled by Charles D. May, M.D., Assistant Professor of Pediatrics, Harvard Medical School, and Charles Upton Lowe, M.D., Blackfan Research Fellow in Pediatrics, Harvard Medical School.

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steatorrheas, and above all, to form a foundation for a rational therapy. These studies were continued by Dr. Shohl assisted by Dr. Shwachman at first, and then, during the war, by members of the resident staff,* and were interrupted by Dr. Shohl's untimely death. The data appeared to be of such general interest that its publication seemed desirable. Critical use of Dr. Shohl's notebooks in conjunction with the hospital records of the patients involved permitted an accurate tabulation of the results of a number of balance periods. These data are presented without analysis at this time. The balance periods and the chemical estimations were performed in the same manner as described in the original report of similar studies.

Details regarding diets, therapy, and the balance data are given in Table I.

OUTPUT PER DAY						NITROGEN RETAINED				
NITROGEN			FECES							
			FAT (GM.)	DRY W/FIGHT (GM. PER KG.)	FAT (%)	GM. PER DAY	GM. PER KG. PER DAY			
TOTAL (GM.)	URINE (GM.)	FECES (GM.)								% NITROGEN ABSORBED
3.12	2.06	1.06	15.1	2.41	52	0.13	0.01	65	1.0	36
4.63	3.80	1.83	23.4	3.83	50	1.19	0.10	60	20	28
5.65	3.03	2.62	-	4.36	-	1.76	0.13	65	42	-
3.74	-	-	23.7	6.25	37	1.08	0.11	-	22	37
-	-	0.35	2.4	1.35	40	-	-	84	-	87
-	-	3.25	23	12.5	41	-	-	27	-	41
5.31	2.17	3.14	5.2	3.42	16	0.69	0.07	50	13	-
5.77	2.58	3.19	-	4.3	-	0.74	0.07	50	11	-
7.15	4.14	3.01	1.8	4.25	4.3	Loss	Loss	70	Loss	-

(Table I continued on following pages.)

A debt of gratitude is owed to Miss Kathleen Scobie, Research Fellow in Nutrition, Department of Maternal and Child Health, Harvard School of Public Health, Boston, for assistance in analysis of diets, and to Miss Barbara E. Duffy and Miss Ardis Paul for technical assistance in the laboratory.

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PROB- ID NO.	PATIENT, AGE	WEIGHT (KG.)	DATE, DAYS IN PERIOD	INTAKE PER DAY					F (G)
				TYPE OF DIET	CALORIES PER KG.	NITROGEN			
						(GM.)	(GM. PER KG.)		
0.	M. C. 22 mo.	10	3/27/44- 3/29/44 2 days	Fat-free milk, low fat solids	52 (Milk only)	4.66	0.47	1	
1.	J. N. 6 mo.	5.6	5/8/45- 5/11/45 3 days	Nutramigen,* pancrea- tin† 1.65 Gm.	130	3.97	0.71	32	
2.	J. N. 6 mo.	6.2	5/15/45- 5/18/45 3 days	Nutramigen, pancreatin 1.65 Gm.	185	5.81	0.94	43	
13.	J. N. 6 mo.	6.3	5/23/45- 5/26/45 3 days	Nutramigen	185	5.57	0.89	43	
14.	J. N. 7 mo.	6.5	6/2/45- 6/5/45 3 days	Nutramigen	115	3.79	0.58	32	
15.	E. M. 3½ yr.	10.0	10/22/43- 10/25/43 3 days	Fat-free milk, ord. low fat solids, sulfadiazine, pancreatin 10 Gm.	93	7.74	0.77	5	
16.	E. M. 3½ yr.	10.0	10/25/43- 10/28/43 3 days	Fat-free milk, ord. low fat solids, sulfadiazine, pancreatin 10 Gm.	58	5.85	0.59	4	
17.	E. M. 3½ yr.	10.0	11/16/43- 11/20/43 4 days	Fat-free milk, ord. low fat solids, pancreatin 10 Gm.	93	7.63	0.76	5	
18.	E. M. 3½ yr.	10.0	11/22/43- 11/25/43 3 days	Fat-free milk, ord. low fat solids, pancreatin 3 Gm.	93	6.84	0.68	5	
19.	E. M. 3½ yr.	10.0	11/29/43- 12/3/43 4 days	Fat-free milk, ord. low fat solids, pancreatin 6 Gm.	83	5.43	0.54	4	
20.	E. M. 3½ yr.	10.0	12/6/43- 12/10/43 4 days	Fat-free milk, ord. low fat solids, pancreatin 1 Gm.	82	4.64	0.46	4	
21.	M. C. 22 mo.	10.0	4/3/44- 4/5/44 2 days	Fat-free milk, low fat solids, pancreatin 1.3 Gm.	52 (Milk only)	4.8	0.48	1	
22.	M. C. 22 mo.	10.0	4/11/44- 4/14/44 3 days	Casein hydrolysate, prod- uct No. 148†	135	6.91	0.69	0	
23.	B. H. 3½ yr.	12.0	11/13/43- 11/15/43 2 days	Casein hydrolysate, prod- uct No. 148, low fat solids	66	3.55	0.29	1	
24.	B. H. 3½ yr.	11.8	12/10/43- 12/12/43 2 days	Casein hydrolysate, prod- uct No. 148, low fat solids	100	4.34	0.36	2	
25.	B. H. 3½ yr.	12.0	11/18/43- 11/21/43 3 days	Casein hydrolysate, prod- uct No. 148, low fat solids, pancreatin 1 Gm.	110	5.72	0.48	2	
26.	B. H. 3½ yr.	12.0	12/1/43- 12/3/43 2 days	Casein hydrolysate, prod- uct No. 148, low fat solids, pancreatin 6 Gm.	117	5.61	0.47	3	
27.	M. C. 22 mo.	10.0	4/16/44- 4/19/44 3 days	Casein hydrolysate, prod- uct No. 148, pancrea- tin, 1 Gm.	135	7.05	0.71	0	

OUTPUT PER DAY					NITROGEN RETAINED				
NITROGEN		FECES			GM. PER DAY	GM. PER KG. PER DAY	% NITROGEN ABSORBED	% NITROGEN RETAINED	% F. RET.
URINE (GM.)	FECES (GM.)	FAT (GM.)	DRY WEIGHT (GM. PER KG.)	FAT (%)					
-	-	4.8	3.3	14	2.36	0.23	-	53	
2.33	0.50	-	2.2	-	1.14	0.20	57	35	
1.72	0.50	-	2.2	-	2.59	0.58	91	62	
1.19	0.55	-	1.86	-	3.83	0.61	90	69	
1.21	0.27	-	0.99	-	2.31	0.26	93	61	
4.56	1.33	4.2	2.7	15	1.55	0.19	83	24	
4.44	1.41	-	2.7	-	0.0	0.0	76	0	
5.05	1.5	1.6	2.6	6	1.08	0.11	80	14	
5.13	1.5	-	2.9	-	0.21	0.02	78	3	
5.18	1.59	-	3.1	-	-1.34	Loss	71	-	
3.64	1.01	-	1.8	-	0.0	0.0	78	-	
-	-	1.6	2.4	6	3.19	0.32	-	66	
-	-	0.97	1.6	6	6.05	0.61	-	87	
2.14	1.17	1.2	1.29	8	0.24	0.02	67	15	
3.04	0.82	-	1.1	-	0.48	0.04	81	11	
2.64	1.32	-	1.8	-	1.76	0.15	77	31	
3.72	1.88	2.7	2.75	8	0.0	0.0	66	0	
-	-	0.4	0.6	7	6.74	0.67	-	96	

TORSION OF THE APPENDIX TESTIS

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ACUTE, painful swelling of the scrotal contents in young boys is seen infrequently. Injury or torsion of the spermatic cord accounts for by far the majority of cases. While trauma may occur at any age, torsion of the cord is seen most often between the ages of 8 and 14 years. Since mumps orchitis seldom antedates puberty, it need not be considered in this group of patients, that is, boys at any age under 12 who are seized with severe pain in the testicle accompanied by inflammatory changes in the scrotum. In a recent communication by one of us,¹ torsion of the spermatic cord was discussed and several cases reviewed.

Torsion of the appendix testis, though rare, is seen sufficiently often to call for its consideration in the differential diagnosis in this group of cases. This discussion and the two case reports are presented in order to bring the subject to the attention of the pediatrician and general practitioner, who usually see these patients first.

The appendix testis, or sessile hydatid (of Morgagni), is attached to the upper extremity of the testis close to or just beneath the head of the epididymis. It is said to be present in about 90 per cent of males, and varies from 5 to 10 mm. in length and less than half as wide. The structure is attached to the connective tissue investing the testis, and consists of vascular connective tissue containing a canal lined with columnar epithelium. Near the end there is frequently found a shallow, funnel-like depression with dentated border, the whole resembling the fimbriated end of the oviduct. The appendices testes are, in fact, the persisting cephalic ends of the embryonic Müllerian ducts, which in the female develop into the oviducts, uterus, and most of the vagina.

In the embryo, the genital ridges, the middle parts of which develop into the testes or the ovaries, arise along the ventromedial surface of the mesonephric kidney. Just lateral to the genital ridges the Müllerian ducts develop. In the male the mesonephric ureters become the genital ducts, and the Müllerian ducts atrophy and disappear except for the caudal ends, which unite and persist as the vestigial prostatic utricle, and the cephalic ends, which persist as the appendices testes.

Torsion of this small, vestigial body produces symptoms often confused with other acute pathology of the scrotal contents or of intra-abdominal disease. The severity of the symptoms may be, and usually are, out of proportion to what might be expected from so small an organ. The early symptoms may be lower abdominal or inguinal pain without scrotal symptoms or gross signs, so that disease within the abdomen may be suspected. Later there is pain in the testicle with exquisite tenderness, edema of the scrotal tissues, and redness of the skin. Because of the extreme tenderness, an accurate examination may be

From the urological department of Watts Hospital.

impossible without anesthesia. The temperature is usually normal or only very slightly elevated. The urine is negative and the white blood count near normal in the early stages, which findings may be especially helpful in ruling out acute infections of the epididymis or testis.



Fig. 1.—Low-power view, showing edema, hemorrhage, neutrophilic infiltration and degeneration of surface epithelium. (Case 2.)

Differentiation from torsion of the spermatic cord may be impossible and for this reason early surgical exploration should be done when either condition is suspected. It is generally agreed that even when the diagnosis can be accurately made, operation should be performed for relief of symptoms and more rapid recovery than can be expected from conservative treatment.

Vermeulen and Hagerty² have recently reviewed the literature and given a description of the microscopic anatomy and pathology of the organ along with the report of two cases. We wish to report on two additional patients recently seen within a period of two weeks.

CASE REPORT

CASE 1.—R. B. R. W., aged 12 years, was admitted Sept. 7, 1946, to Watts Hospital, and discharged Sept. 13, 1946.

This 12-year-old white boy was first seen on Sept. 7, 1946, complaining of painful swelling of the left side of the scrotum of about twenty-four hours' duration. There was the history of slight trauma to the region two days before with transient pain at the time,



Fig. 2.—High-power view of small vessel containing a hyaline thrombus, and surrounded by a cuff of neutrophilic leucocytes. (Case 1.)

otherwise the history was entirely negative. The temperature was 99.2, pulse 88, respiration 20, and the blood pressure 100/64. General examination revealed no abnormal findings but the left side of the scrotum was edematous, red, and exquisitely tender. Details of the scrotal contents could not be distinguished because of the extreme pain and tenderness, but the testis felt enlarged and there was a suggestion of a firm mass at upper pole of the epididymis. The right scrotal contents appeared normal. The urine was normal and the leucocyte count 5,800.

The impression was that of torsion of the spermatic cord and operation was decided upon. Under avertin and ether anesthesia the left side of the scrotum was incised and the structures explored. On opening the tunica vaginalis a small amount of cloudy fluid escaped. The appendix testis was very dark and swollen and as it lay exposed was seen to untwist. Its pedicle was ligated and it was removed. The testicle, epididymis, and spermatic cord were found normal.

The postoperative course was uneventful and the patient was discharged on the sixth postoperative day.

Pathologic Report.—"Torsion of appendage testis with secondary infarction."

Microscopic Description.—"Sections of the specimen reveal a structure consisting mostly of acute exudate and granulation. There is an epithelial lined space, the cells of which are of the columnar type."

CASE 2.—H. G. M., Jr., aged 10 years, was admitted to Watts Hospital Sept. 21, 1946, and discharged Sept. 26, 1946.

This 10 year-old white boy came to our attention on Sept. 21, 1946, with complaint of some pain in the right inguinal region and right lower abdomen for the past four or five days. On the evening before admission the right testis had become painful and upon examination by his parents was found to be swollen and tender. This had increased to some extent when seen the following day. Physical examination: Temperature 99.4; pulse 80; respiration 20; blood pressure 100/70. The general examination was entirely negative. The right side of the scrotum was edematous, red, and exquisitely tender, so that accurate palpation of its contents was not possible, but the testicle felt enlarged. The epididymis could not be isolated. There was some tenderness along the spermatic cord. The left scrotal contents were normal. The urine was found normal and the leucocyte count 9,800.

Impression at the time was that of torsion of the appendix testis, though torsion of the spermatic cord could not be ruled out, and immediate operation was decided upon.

Ether anesthesia was given, and on opening the tunica vaginalis some free, blood-tinged fluid was found, and attached to the globus major of the epididymis was a gangrenous mass about one centimeter in diameter with a small twisted pedicle. The pedicle was ligated with fine catgut and the mass removed. The testis was normal in color and consistency and there was no evidence of torsion of the spermatic cord.

The postoperative course was uneventful and the patient was discharged on the fifth postoperative day.

Pathological Report.—"Torsion of appendage testis."

Microscopic Description.—"The fragment is covered by a single layer of epithelial cells while the central mass of tissue represents hemorrhage and exudate compatible with torsion."

COMMENT

Just why the pedicle of the appendix testis should become twisted and thus produce strangulation is not clear. It must be assumed that in most cases the pedicle is abnormally long and twisting is produced by some sudden, violent movement of the testicle. Torsion of the spermatic cord occurs under similar conditions. Therefore, in either case there is likely to be the history of injury. The patient may feel the acute pain of torsion on jumping on a bicycle or at the time of some strenuous movement as in a football game. He thinks he has injured himself and reports to his parents. A case of torsion of the spermatic cord in a doctor's son was denied surgery for several days with resultant loss of the testicle because the father was convinced that the boy injured himself while playing basketball. So the history of injury must often be discounted. Torsion of the appendix testis can seldom be accurately distinguished from torsion of the spermatic cord and for that reason prompt surgery in suspected cases is recommended.

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MEGALOBLASTIC ANEMIA IN INFANCY

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IN RECENT months the term megaloblastic anemia has made its appearance in the literature; it was proposed by Zuelzer and Ogden¹ for a macrocytic anemia which occurs commonly in infants, but previously had been difficult to classify properly. The important therapeutic aspect of this condition is its tendency to respond specifically to folic acid.

For a number of years it has been observed that certain macrocytic anemias of childhood were responsive to crude liver therapy, but only recent studies have demonstrated that the erythrocytic maturation factor contained in liver is also found in folic acid (synthetic lactobacillus casei factor).² Peterson and Dunn³ have shown that true pernicious anemia is rarely seen in infancy and childhood, and that it differs from other macrocytic anemias (including megaloblastic anemia) in that pernicious anemia is always accompanied by histamine-resistant, gastric achlorhydria, and necessitates continuous therapy to maintain a continuous remission. Information available at the present time indicates that megaloblastic anemia is a temporary deficiency of the antianemic principle.⁴

Clinically, this condition is most often seen in infants between 2 and 16 months of age. The child suffering from megaloblastic anemia usually exhibits marked pallor, weakness, irritability, persistent upper respiratory infection, and extreme loss of appetite. He may have fever and gastrointestinal disturbances. Physically, the most outstanding finding is the extreme pallor; he is likely to be emaciated, and may present a palpable spleen and petechiae. Sex distribution is about equal; the condition has not been seen in the Negro race.

Laboratory studies reveal these infants to have a severe normochromic anemia with many macrocytes, but the mean cell diameter may not exceed the normal figure, due to the concomitant presence of numerous microcytes. There is a tendency toward leucopenia and thrombopenia. Bone marrow study shows erythropoiesis to be definitely megaloblastic. After therapy has been instituted, there is a characteristic reticulocyte response seen in the peripheral blood similar to that seen in addisonian pernicious anemia.

CASE REPORTS

CASE 1.—D. R., a white boy 6 months of age, was admitted to Memorial Hospital, South Bend, Ind., Nov. 7, 1946, because of pallor, failure to gain weight, and marked loss of appetite.

He had weighed 5 pounds, 10 ounces at birth, and had progressed normally until 1 months of age, when he weighed 12 pounds, 10 ounces. At this time he had an upper respiratory infection characterized by frequent episodes of coughing with occasional vomiting. A month later he had developed marked anorexia and noticeable pallor; and an examination of his blood revealed the following findings: hemoglobin of 9.7 Gm.; erythrocyte count of 2,730,000 per cubic millimeter; and white blood cell count of 3,850 per cubic millimeter, with 23 per cent neutrophils, 71 per cent lymphocytes, 1 per cent monocytes,

and 5 per cent eosinophiles. Iron in the form of ferrous sulphate was administered during the following month, but, when the infant was seen then, he had gained only one ounce, was refusing most of every feeding, and vomiting freely. Another examination of the child's blood showed the hemoglobin to be down to 6.2 Gm.; the erythrocyte count to have dropped to 1,710,000 per cubic millimeter; and the white blood cell count to be 6,600 per cubic millimeter. He was hospitalized at this time.

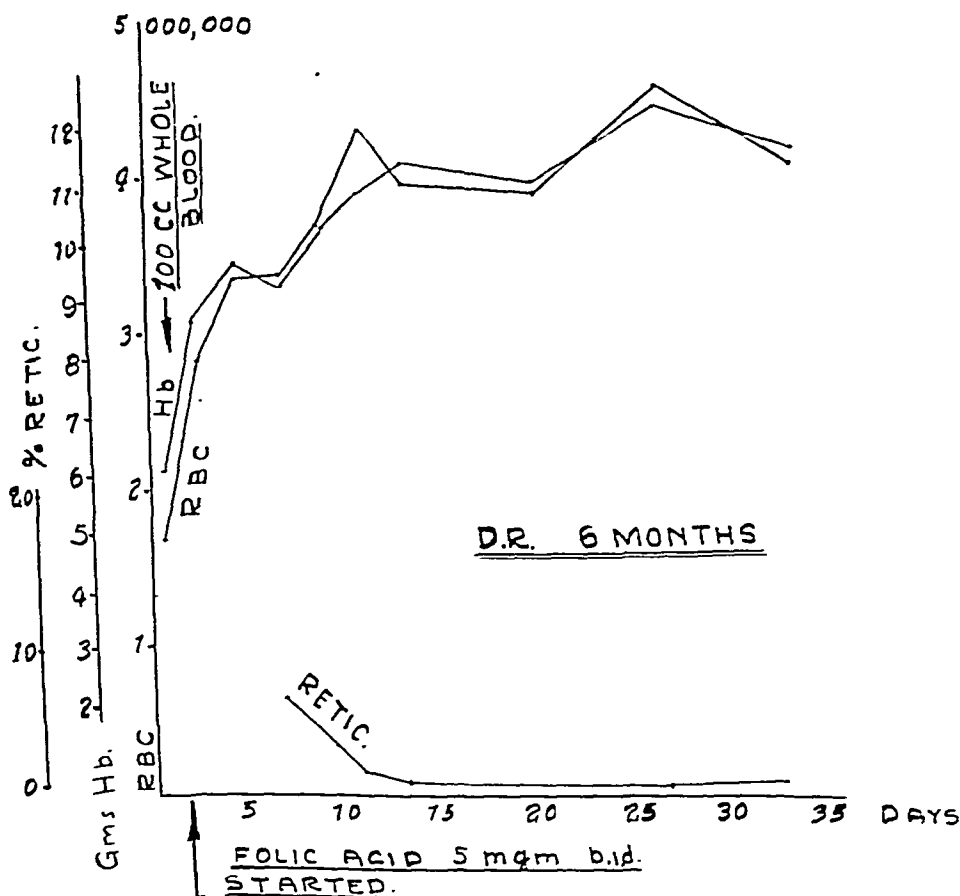


Fig. 1.—Response to folic acid in Case 1.

Physical examination on admission revealed the infant to be listless, pale, and irritable. His spleen was not palpable, and his liver was a normal size. All other findings were normal.

During his hospital stay of eleven days there were several hematologic studies made which are presented in graphic form (Fig. 1). The mean red cell diameter ranged from 7.8 to 8.0 microns, and there were 640,000 platelets per cubic millimeter. Examination of tibial marrow was done, and the following findings were reported by the pathologist: "... a preponderance of nucleated red cell elements, the majority of which appear to be in the megaloblastic (erythroblastic) stage. There is also a large number of primitive reticulum cells. There are likewise many smudge forms. Granulocytic elements are rather rare. Megakaryocytes are exceedingly rare. There is no evidence of metastatic tumor, and the impression is of a marrow showing megaloblastic hyperplasia."

Folic acid therapy was instituted; 5 mg. were given orally twice a day, and because considerable concern was felt regarding the baby's condition, it was decided that 100 c.c. of whole blood should be given also. Through an oversight on our part, reticulocyte counts were not done during the first few days. They were, however, obtained in time to demonstrate a definite reticulocyte response to the administration of the folic acid.

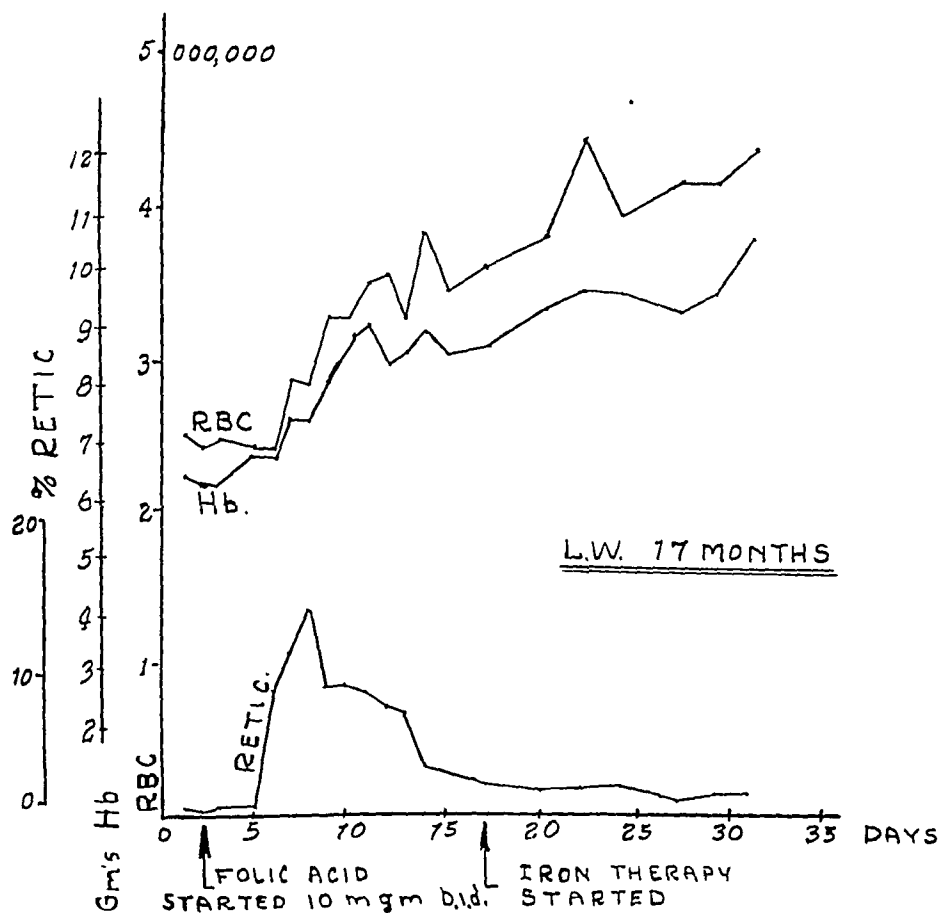


Fig. 2—Response to folic acid in Case 2. Includes period of hospitalization only.

By the end of the short period of hospitalization, this baby, who had required approximately one hour to take a few ounces of formula prior to admission, was eating with vigor, had become much more active physically, and was no longer irritable. He was discharged from the hospital Nov. 18, 1946, and has been followed closely until the present time. Frequent blood examinations have been done, and they have all shown the hemoglobin and red blood cell count to be within normal range. Folic acid was administered for a period of four months. At one year of age (six months after the child's illness) he weighed 20 pounds, 1 ounce, and was perfectly healthy.

CASE 2.—L. W., a white girl 17 months of age, was admitted to Memorial Hospital, Jan. 28, 1947, because of pallor, diarrhea, loss of appetite and failure to gain.

Although the parents were not certain about the child's birth weight, they thought she had weighed about 8 pounds, and stated that she did well until 5 months of age. She

had received cod-liver oil since one month, and orange juice was started at three months. The first unusual occurrence the parents noticed was the presence of an upper respiratory infection which recurred repeatedly. She soon began to refuse feedings and failed to gain weight. Her formula had been changed many times, but she failed to improve.

In September, 1946, at one year of age, she had been acutely ill with a severe diarrhea, and was hospitalized in another hospital in this city. Her condition was critical and she received several blood transfusions. She was thought to be suffering from a gastrointestinal sensitivity to cow's milk, and as a result cow's milk was replaced with goat's milk in her diet, but improvement was only temporary. Since that time her condition had changed little.

Upon physical examination she was found to be extremely emaciated (weight was 14 pounds, 6 ounces), unable to sit alone, very pale, irritable, mildly dehydrated, and her temperature was 101.8° F. rectally. Her abdomen was enlarged, and almost all subcutaneous fat was absent. She had a severe ulcerative stomatitis; her spleen was not palpable. Other findings were normal.

Laboratory examination of her blood revealed the hemoglobin to be 6.4 Gm.; erythrocyte count was 2,520,000 per cubic millimeter; and white blood cell count was 4,400, with 33 per cent neutrophils, 61 per cent lymphocytes, one per cent eosinophiles, and 5 per cent monocytes. The mean red cell diameter was 8.2 microns, and there were 550,000 platelets per cubic millimeter. Many further blood examinations were made during the child's hospital stay, and these are presented in graphic form (Fig. 2). Tibial marrow was studied, and the following findings were reported by the pathologist: ". . . numerous degenerated nuclei, the so-called smudge cell. The erythroid elements are normal; but only a rare normoblast, that is, one showing hemoglobin in its cytoplasm, can be seen. Most of the erythroid elements are observed to be at the megaloblastic or early erythroblastic stage. . . Pathologic Diagnosis: Bone marrow showing red cell maturation at megaloblastic level."

Within a few hours after her entrance into the hospital it was learned that she would not take enough food and liquids voluntarily to maintain her fluid balance, so for the first four days she was fed by gavage. 15,000 units of penicillin was given intramuscularly every three hours for four days, and the stomatitis and diarrhea improved.

Folic acid therapy, 10 mg. orally twice a day, was instituted the day following admission. It was decided that this child should not receive a blood transfusion until the response to folic acid could be observed. As it turned out, the transfusion was unnecessary. A prompt reticulocyte response was demonstrated, followed by a gradual rise in hemoglobin and red blood cell level. On the seventeenth hospital day, when the hemoglobin rise seemed to be slow, iron therapy in the form of ferrous sulfate was started in an effort to overcome any hypochromic anemia which might be present.

She continued to improve hematologically as well as clinically, and was discharged from the hospital Feb. 28, 1947, the thirty-first hospital day, at which time she was eating well, gaining weight, sitting up, and was much less irritable.

Inasmuch as this child lives out of the city and it is difficult for her parents to bring her in for follow-up study, close observation has been impossible. However, she was seen recently, July 29, 1947, and at that time weighed 23 pounds, 12 ounces (a gain of 9 pounds, 6 ounces in six months), and improvement was marked. She had acquired the ability to walk and talk, and was eating a well-balanced diet eagerly. Blood examination revealed a hemoglobin of 11.4 Gm. and a red blood cell count of 4,600,000 per cubic millimeter. Folic acid was administered over a period of three months.

SUMMARY AND CONCLUSIONS

Recent articles appearing in the medical literature pertaining to megaloblastic anemia in infancy are reviewed briefly.

Two cases which have been seen in the past ten months are presented.

It is to be noted that neither of these two patients demonstrated splenomegaly or thrombopenia, both of which are said to be seen frequently in this condition.

Megaloblastic anemia is a relatively common disease of white infants, and, since a complete and permanent recovery can be effected by folic acid therapy, the condition should be understood by all those caring for small children.

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SILVER NITRATE STENCIL STAINING FOR IDENTIFICATION OF NEWBORN INFANTS

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THE purpose of this report is to recommend an easy method of identifying nursery babies by the use of silver nitrate stain or impregnation.

A mixup of infants in any nursery can be a very grievous event to the hospital and to the families concerned. The reputation of the hospital is jeopardized by undesirable publicity, aside from the possibility of legal action.

The majority of nurseries try to avoid such events by the use of various identification systems. These systems are: (1) ink pad impressions of the newborn infants' feet for the hospital record and infants' birth certificate; (2) beads with the babies' or mothers' name and, perhaps, room number; (3) adhesive tape having ink stamped lines for the pertinent information stuck on the infants' backs; (4) ultraviolet exposure through identification letters

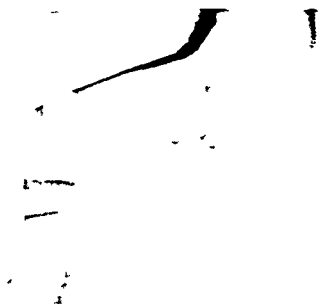


Fig. 1.



Fig. 2.

Fig. 1—Original stencil impregnation.

Fig. 2—Two weeks later, showing letters still visible.

In checking the security of the first system, it is well known that the footprints do not identify the baby when it comes time to bring him to the mother. Qualified fingerprint experts or readers are practically never available to classify the imprint in the hospital at that time. There have been a few cases where the wire for beading the beads has broken, resulting in loss of the beads. The adhesive tape writing often becomes illegible by the running of the letters due to urine or moisture soakings. The ultraviolet system is a good system if it does not burn or lead to impetigo or skin rash.

It is well known that silver nitrate will stain the skin black and remain on the skin for a period of two weeks or more in spite of daily washings.

With this fact in mind, and the use of a commercial brass stencil plus cotton applicators, the usability of the silver nitrate for identification purposes was studied.

Thirty per cent silver nitrate is the percentage found most suitable. The stencil is placed on the buttocks or the feet and slight pressure is exerted to cause the skin to protrude through and above the stencil surface. A cotton applicator is moistened, but not soaked with the silver nitrate solution, and then rubbed on the protruding skin. If any oozing is noticed, a dry cotton applicator is immediately applied to absorb it. Better results were noted when some of the brass stencil was touched, for it makes the stain deepen and darken faster.

It is suggested that the same letters used on the infant can be used on the mother's hip while she is still on the delivery table.

Since the stain gradually peels off after fourteen days, it has served its purpose and given added security to the hospital and the parents.

The method is simple, economical, and offers security to the public and the hospital.

Case Reports

INFANTILE CORTICAL HYPEROSTOSIS

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AS SUGGESTED by Caffey^{1, 2} and by Smyth,³ the recently described, newly recognized syndrome of infantile cortical hyperostosis is probably not as uncommon as is indicated by the few reported cases. Both authors advance considerable evidence to support this suggestion and have described sixteen cases since the syndrome was first recognized in 1945. Since then, there have been several other individually reported cases (Whipple⁴ and Dickson, Luckey, and Logon⁵). It is the purpose of this case report to call attention to (1) the prominent signs and symptoms; (2) the present status of etiology; and (3) to discuss current therapeutic measures.

CASE REPORT

R. G., a 4-month-old male infant, was admitted to the Springfield Hospital Aug. 4, 1946, because of fever, irritability, and brawny facial edema.

Family History.—Parents are in good health. There is no known history of metabolic disturbance, tuberculosis, or syphilis.

Birth History.—Para i, gravida i. Delivery was normal, with no instruments used. Birth weight was 7 pounds 11 ounces. Mother had adequate diet during pregnancy, well fortified by the addition of vitamins. There was no history of rubella or other virus disease during the pregnancy.

Past History.—According to the mother, who is a registered graduate nurse, this infant has been in excellent health until the onset of the present illness. His growth and development since birth fell in the 90 percentile group. His diet consisted of a modified evaporated milk formula with the addition of adequate amounts of concentrated synthetic vitamins A and D, and adequate amounts of strained orange juice diluted with cooled, sterile water.

Present Illness.—Ten days prior to admission, the patient developed what seemed to be a typical case of an upper respiratory infection prevalent in the community at the time. This was characterized by fever, irritability, rhinitis, and an occasional dry, unproductive cough. An attending physician prescribed fluids, aspirin, and a dilution of the formula. The patient failed to respond to these measures. The temperature persisted at 101° to 102° F. and although the rhinitis and cough subsided, the symptoms of irritability became more evident. The day before admission to the hospital, the mother noted a brawny, bilaterally equal swelling of the lower jaw. At this time examination revealed minimal pharyngitis and bilateral catarrhal otitis media.

On admission to the hospital a throat culture was taken and the patient started on sulfadiazine, 1 grain per pound a day on a four-hour schedule. Because of the obvious facial and cervical edema, a visual and digital examination of the throat was made but no evidence of supraglottic edema or hypertrophy of the tonsils was found, nor did the clinical picture indicate any obstructive pharyngeal lesion.

Physical Examination.—The significant physical findings at time of admission were as follows: The patient was a well-nourished and well-developed,

From the Pediatric-Out-Patient Department, Springfield Hospital.

4-month-old male infant falling above the 90 percentile group on the developmental grid. He did not appear acutely ill but was markedly irritable on handling, especially when the face and jaw were touched. The face presented a moderate brawny edema, bilaterally equal. The skin was clear. The nasal mucous membrane was mildly injected as was the mucous membrane of the pharynx.

Neck.—Although the edema seemed to extend somewhat into this region, palpation failed to reveal any adenopathy or soft tissue induration. There was no real nuchal rigidity, but the patient objected vigorously to any movement of the neck.

Chest.—Examination of the chest revealed rapid but equal respiratory movements. The lungs were clear and resonant throughout. The heart was normal in size and position and auscultation failed to reveal any abnormality.

Abdomen.—Negative. The abdomen was soft throughout, the spleen edge barely palpable, and the liver not palpable. No abnormal masses were felt.

Extremities were negative.

Neurologic.—The neurologic examination failed to reveal any abnormalities. The knee jerks were active. No Babinski or Kernig sign was present. The anterior fontanelle was open but not tense. Appraisal of mental status using Gesell standards gave findings which were well within normal limits in so far as motor, language, personal, and social behavior were concerned.

Laboratory examinations on admission gave the following data:

Throat culture: *Staphylococcus aureus* was the predominant organism

Blood Count: Red blood cells-----4,850,000

White blood cells-----19,500

Hemoglobin -----77% 11.1 Gm.

Differential -----69% neutrophils

28% lymphocytes

3% eosinophiles

Lumbar Puncture: Fluid clear, no increase in pressure

Dynamics normal

9 cells: (5 lymphocytes, 4 polymorphs)

Sugar, 62 mg./100 c.c.

Pandy negative

Culture and smear negative for bacteria

Urinalysis: Negative

Progress.—Despite the sulfadiazine therapy, the febrile course continued. The daily range of fever was from 99° to 102° F. with a tendency toward daily evening elevations. Sulf crystals appeared in the urine and by the end of the second week of hospitalization, it was necessary to discontinue the drug. At this point, penicillin was started in dosage of 20,000 units intramuscularly, every three hours. Penicillin in this dosage was continued for three weeks without affecting the course of the disease. During the next two weeks, 40,000 units of penicillin were given intramuscularly every three hours, then 50,000 units every three hours for another week without in any way altering the course of the disease. Since penicillin seemed to be of no value in this case, it was discontinued. Smyth³ first suggested that penicillin might be of value in this illness, but to the author's knowledge this is the first case in which it has been tried.

Growth and Development.—The patient's weight gain continued uninterrupted during the entire stay in the hospital, which totaled thirty-eight days.

Temperature.—The temperature elevation throughout the entire stay in the hospital continued fluctuating between 99° and 102° F. unchanged by any of the therapeutic endeavors.

Bacteriology.—Repeated throat cultures showed *Staphy. aureus* and because of the possibility that this microorganism might be associated with abnormal calcium metabolism, Foley⁶ undertook a study of the microorganism

at the Department of Pathology and Bacteriology of the Massachusetts General Hospital. After considerable investigation, it was apparent that this micro-organism did not utilize calcium or its salts and could in no way be considered as the etiologic agent of this case.

An elimination diet plus an antihistamine drug was tried. The diet consisted of evaporated goat's milk, oatmeal, banana, 100 gm. of ascorbic acid, 20 drops of concentrated vitamins A and D, benadryl (10 mg.) was given three times daily. This allergic regime was maintained for one week with no apparent effect on the clinical course of this patient except for a slight loss of weight. It might be well to point out that there was no familial history of allergy. On one occasion a blood count showed 9 per cent eosinophiles. Several other counts showed 3 or 4 per cent eosinophiles. Although this trial may well be inadequate, it nevertheless seemed that allergy played no part in the etiology or therapeutic approach to this disease.

Roentgen examination of the mandibles during the first week in the hospital failed to reveal any abnormality. During the fourth week a tender swelling was observed over the left clavicle by the nurse. Because of this finding, repeat skeletal roentgenograms were taken and these now showed scattered hyperostosis in both clavicles, mandibles, and several ribs.

One week later, roentgenograms were taken by Dr. Edward B. Neuhauser of the Children's Hospital, Boston, Mass. The following is Dr. Neuhauser's report (Figs. 1, 2, 3, and 4).

X-ray Report.—Examination of the skeleton shows no definite abnormality of the calvarium, which appears to be normal in size and contour. The bones are well calcified and are of average density and show apparently normal architecture. The maxilla shows nothing unusual, but there is marked abnormality of the mandible, which shows extraordinary subperiosteal new bone formation which appears to be at least 1 cm. in thickness. The new bone is rather amorphous in structure and varies very slightly in density. In places there does appear to be slight lamellation of the new bone. The margins of the new bone are somewhat irregular in contour. There is a similar change about each clavicle with extensive subperiosteal new bone formation which appears to be most prominent in the outer half of each clavicle, and here, too, the new bone is amorphous and irregular in contour.

Nearly all of the ribs show similar change and this change appears to be most marked in the anterior third of the ribs. There is no evidence of any destruction and, on these films, no evidence of any underlying pleural thickening or pleural effusion.

The bones of the spine and long bones show no essential variation from the normal.

Examination of the chest shows no definite abnormality of the heart. There is considerable prominence of the anterior superior mediastinum, both to the right and left, presumably due to moderate prominence of the thymus. The lungs show nothing unusual. The soft tissues of the abdomen show no definite abnormality.

The changes are those of infantile cortical hyperostosis.

Clinical.—The clinical course of the patient during the hospital stay was characterized by continued irritability, exaggerated by handling the face or upper extremities, a continued low-grade fever, and facial edema.

Growth and development as measured by weight, height, chest, head, and abdomen measurements progressed unaltered in the 90 percentile group throughout the thirty-eight-day stay in the hospital.

Laboratory studies indicated a rapidly developing anemia as there was a drop in the hemoglobin and red blood cell count on two occasions to below 9



Fig. 1.—Mandible showing extraordinary subperiosteal new bone formation.



Fig. 2.—Another view of the mandible seen in Fig. 1.



Fig. 3.—Lateral view of mandible showing subperiosteal formation plus amorphous nature of this formation.

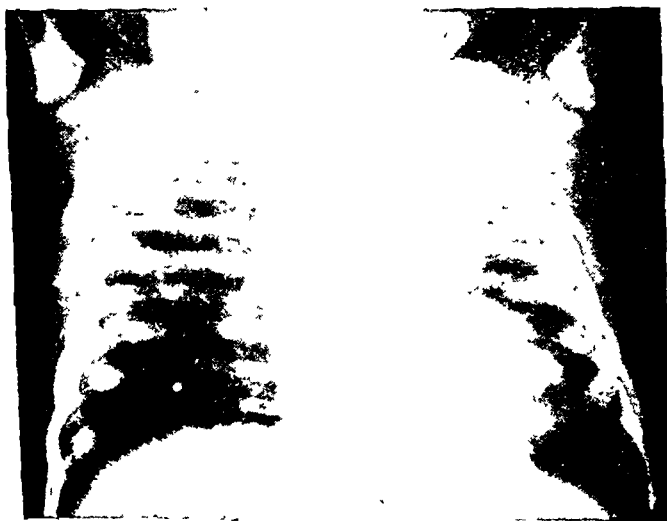


Fig. 4.—New bone formation of clavicles. Here again the amorphous irregular characteristic is evident. The ribs show similar changes.

Gm. per cent and 3,000,000 respectively. The anemia was improved by the administration of properly typed blood on both occasions.

There was a constant leucocytosis throughout the entire course, ranging from 15,000 to 22,000. The differential remained unaltered and a typical differential was polymorphonuclears 54, lymphocytes 37, eosinophiles 3, monocytes 6. Other hematologic data were: prothrombin time, 18 seconds as compared with a control of 15 seconds; clot retraction time, two hours, complete within four hours; clotting time, 4 minutes; bleeding time, 2 minutes; platelets, 363,000; blood vitamin C, calcium, and phosphorus were normal.

Serologic examinations, including blood Wassermann, agglutination tests with S typing, paratyphoid A, paratyphoid B, *Brucellus abortus* and heterophile agglutination were negative.

The patient was discharged from the hospital on the thirty-eighth day. Follow-up over a six-month period showed slow but definite diminution of the facial edema and the masses over the clavicles. Roentgenographic follow-up also showed a diminishing of the roentgenographic changes and a slow return to normal appearance of the bones involved.

The temperature record showed a persistent elevation over this entire six-month period but tended toward a lower level. Hemoglobin determinations and red blood cell counts at monthly intervals failed to indicate any recurrence of the anemia. The patient during this time was fortified with an iron preparation in appropriate amount. Growth and development continued unaltered in the 90 percentile group. A mental growth development well within normal limits was maintained.

Comment.—All of the reported cases of infantile cortical hyperostosis, as well as the above reported case, fail to indite the birth, the diet of the mother, or maternal heredity. From the literature, one gets the impression that an upper respiratory infection may be responsible for precipitating this syndrome and in this case there is seemingly a definite association. Syphilis seems not to be the etiologic agent. That this disease is a metabolic disorder has been repeatedly suggested, but all studies so far failed to advance any proof.

The most striking clinical observation in nearly all of the reported cases was the similarity in the facial appearance of the patient when the mandible was involved. This characteristic is so consistent that the diagnosis probably could be made by a glance at the photographs of a patient suffering from the disease. (Fig. 5).

Persistent fever is present in all cases, and in the reported case persisted as long as six months after the onset.

Irritability very similar to the type seen in scurvy is an ever-present symptom. Like scurvy, it seems to be due to the pain experienced when the affected parts are moved. When left undisturbed, the patient seemed quite content, but passive motion of any sort quickly brought on the typical irritability. This symptom, too, persisted for many months.

Anemia seems to be a constant feature and transfusions are necessary in a few of the cases of this disease. Iron and high vitamin diets, as well as transfusions, were used symptomatically in this case.

An observation which has not been recorded in the literature, but which was most impressive in the present case, is that despite fever, anemia, and roentgenographic changes, the patient's growth and development proceeded unaltered. It is unusual that any disease of many months' duration, whatever its etiology, would not interfere with normal growth and development.

The visible swellings over the clavicles in this case were tender to touch, and as in Caffey's case¹ seemed to make their appearance suddenly. This patient was under constant observation, but not until the thirty-seventh day of

the disease did the swelling appear. The mandibular swelling involved the entire mandible up to the lower eyelids. The swelling receded slowly and took nearly five months to disappear.

Caffey² writes that soft-tissue swellings over bones other than the mandible do not occur, but in this case there was definite, easily observed, and palpable swelling over the left clavicle, but none over the right clavicle. X-ray revealed involvement over both clavicles, more marked on the left. There was no palpable swelling over the ribs, which showed roentgenographic evidence of hyperostosis.



Fig. 5.—Showing characteristic facial appearance of infant with mandibular involvement.

The only positive laboratory data found in the reported cases and in this case were: (a) a progressive anemia which in several of the reported cases and in this case required small repeated blood transfusions; (b) leucoeytosis; (c) slightly elevated phosphatase.

The vitamin C blood determinations, the calcium and phosphorus studies were all normal.

No biopsy was done in this case, but detailed microscopic studies of the bone and the surrounding soft tissue have been done by Smyth³ which revealed degenerative changes of the muscle overlying the hyperostosis. This was of a fatty, fibrinous character. No evidence of inflammatory processes or subperiosteal hemorrhage was noted.

The roentgenographic findings have been fully and excellently described by Caffey.² External thickening of the cortical portion of the bone is characteristic. This may or may not be laminated and extends the entire length of the corticalis except for the terminal segments of the shaft. The extraordinary subperiosteal new bone has been observed in all cases.

The course usually is prolonged, as in the present case, which ran a course of six months. However, the outcome in all cases was favorable. The activity in the affected bones subsided, leaving no apparent residual.

CONCLUSION

A case of infantile cortical hyperostosis is reported in a 4-month-old male infant. The diagnosis was made on the clinical findings of fever, irritability, anemia, characteristic facial brawny edema and roentgenographic evidence of hyperostosis of the mandible, ribs, and clavicle.

Attempts to prove *Staph. aureus* as the etiologic agent by means of bacteriologic study of its utilization to calcium proved futile. The etiology of this disease is still undetermined.

Penicillin and sulfadiazine were given an adequate clinical trial, but did not influence the course of the disease.

An extensive trial with the use of antihistamine preparation and an elimination diet was without success.

Attention is called to the unaltered growth and development of the patient throughout the entire prolonged course of the disease.

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ERYTHROBLASTOSIS FETALIS IN A PREMATURE INFANT FROM A MOTHER WITH SICKLE CELL ANEMIA

A REPORT OF A PATIENT SUCCESSFULLY TREATED BY EXCHANGE TRANSFUSION

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FETAL erythroblastosis is relatively uncommon in Negro infants since the incidence of Rh negativity among Negro women is only about half as great as among white women.^{1, 2} Uncommon also is the production of a viable infant by a woman with active sickle cell anemia, and multiple successful pregnancies are extremely rare. The present case report deals with a premature Negro infant with erythroblastosis fetalis (icterus gravis) produced by the third pregnancy (second living child) of an Rh-negative Negro woman with active sickle cell anemia. The infant was successfully treated by exchange transfusion. As far as can be determined by our review of the literature, this particular combination of circumstances has not been previously reported.

CASE REPORT

Baby F., a male Negro infant, was born in St. John's Hospital on May 1, 1947. The baby's mother is a 32-year-old Negro woman who had had two previous pregnancies. The first, in 1932, resulted in a still-born macerated fetus whose length of gestation is not known. The second pregnancy was in 1933 and resulted in a full-term infant who survived and is alive and well today. In 1937, the mother was hospitalized for the first time because of severe right upper quadrant pain, jaundice, and vomiting. A diagnosis of cholelithiasis was made, but the gall bladder, when removed, was found to be normal and without stones. Blood serologic tests for syphilis were reported positive at this time, and arsenical therapy was begun. In 1939 she was again hospitalized, this time for right lower quadrant pain, and an appendectomy was performed. The pathologists report was "chronic appendicitis." She received one transfusion during her stay in the hospital at that time. In October, 1939, she was admitted to St. John's Hospital and the diagnosis of sickle cell anemia was made for the first time. She was again transfused and since that time has had frequent severe hemolytic crises which have necessitated more than 60 additional transfusions up to the present. In January, 1947, she was readmitted on the Gynecological Service because of severe pelvic pain, and a diagnosis of sickle cell crisis with pregnancy was made. Her last menstrual period was not definitely remembered but occurred in August or September, 1946. Throughout January she threatened to abort, having frequent strong uterine contractions and passing frequent clots. She was sedated and transfused several times. Severe transfusion reactions occurred and Rh typing showed her to be Rh-negative. Anti-Rh titration was not done.

In March she was again admitted to another hospital and additional transfusions were administered. She was readmitted to St. John's Hospital and on May 1, 1947, delivered a living male infant spontaneously by footling breech presentation after a prolonged labor characterized by inertia.

The baby was a small, well-developed premature boy weighing 4 pounds, 8 ounces. He was markedly cyanotic at birth, but after resuscitation and the

administration of oxygen he responded well and cried fairly vigorously. He appeared faintly jaundiced. The tip of the spleen was just palpable, but there were no other abnormalities noted except for the presenting left leg, which was edematous and blue.

Three hours after birth the jaundice was fairly marked. Blood workup at this time showed: blood type O, Rh-positive; icterus index, 42.8; RBC 4.9 million, hemoglobin 14 Gm., WBC 8,950.

The stained smear showed a normal white cell differential, with 17 erythroblasts per 100 white cells. Sickling was not present, either in the stained films or in the wet preparation. The Hinton and Wassermann tests were subsequently reported negative.

Exchange transfusion was decided upon and the procedure was carried out approximately nine hours after birth as soon as type O, Rh-negative blood could be obtained. During this interval the infant had one severe cyanotic attack which was relieved after suction of the trachea and the administration of carbogen and caffeine.

Transfusion Method.—The infant was placed in a heated crib with the head and the right leg exposed and accessible. The leg was firmly strapped to a padded board. A cut-down was done at the ankle and the saphenous vein exposed. A No. 22 gauge blunt needle was inserted in the vein and the other end connected via a three-way stop-cock and syringe to a flask containing 250 c.c. of citrated whole blood, type O, Rh-negative. The transfusion was then started and continued by drip or push depending on the rate of flow desired. After the transfusion was begun, a No. 19 gauge short-bevel fontanel needle was inserted into the superior longitudinal sinus through the posterior angle of the anterior fontanel, and the curved block attached to the needle was maintained in close approximation to the scalp. The stylet of this needle was removed at intervals and 20 c.c. of blood were aspirated each time. This was repeated ten times. After the 200 c.c. had been removed, the transfusion was completed by the administration of the final 50 c.c. of blood, the rates of injection and withdrawal having been kept as equal as possible. Heparin was not used. The infant withstood the procedure well and was returned to his incubator in good condition.

Subsequent Course.—Immediately following transfusion, Rh typing was repeated and was only very weakly positive with a few small clumps, whereas previously the agglutination had been marked. The following day the baby appeared to be more jaundiced but otherwise his clinical condition was good. He was started on a Similac formula which he soon took well. On the third day jaundice was marked and the icterus index had risen to 150. By the fifth day it had reached 200, but in spite of this the baby was thriving and had started to gain weight. On this date the red cell count was 5.75 million and the hemoglobin was 15.4 Gm. There were now 3 normoblasts per 100 white cells. No sickle cells were present. The Rh agglutination was very weakly positive as before.

From this point on there was a gradual drop in the red count and hemoglobin throughout the next month. The low point was reached on June 10, when the red count was 2.55 million and the hemoglobin 6.8 Gm. However, by this time the clinical jaundice had disappeared and the icterus index had dropped to 10. Rh typing now showed strongly positive agglutination. In spite of the low blood count the baby was doing well. His weight was now 6 pounds and he was gaining steadily. Repeated sickling preparations failed to demonstrate any definite sickle cells.

During the next month there was a slow, gradual rise in the red cell count and hemoglobin without further transfusion or the administration of hematinics.

On July 15 the red count was 3.87 million and the hemoglobin 9.4 (gm. The weight was 7 lb., 8 oz. The infant now appears to be developing normally in all respects. The spleen is not palpable. There is no neck retraction or athetosis. He appears bright, strong, and alert. The peripheral blood still shows no sickling.

COMMENT

Exchange, substitution, or exsanguination transfusion, as it is variously termed, is now being employed with increasing frequency in the treatment of erythroblastosis fetalis with apparent improvement in the prognosis. Three general techniques have been employed, utilizing, (1) fontanel taps for removal of blood according to the method first described by Wallerstein,³ (2) section of the radial artery (Weiner)⁴ or (3) both the injection and withdrawal of blood through the umbilical vein (Diamond).⁵ The last method appears to possess certain advantages, particularly the elimination of the surgical aspects of the procedure, but, of course, must be carried out soon after delivery.

Various methods have been employed to calculate indirectly the exact percentage of replacement of the infant's blood that can be obtained by exchange transfusion.³ Had sickleemia been present in this case, the sickle cells might have served as admirable "tracers," and from the relative number present prior and subsequent to transfusion, a calculation of the percentage of exchange might have been made. But they did not appear in this child. That a substantial exchange was effected is apparent from the weakening of the Rh agglutination, the majority of the Rh-positive cells having been removed. Two hundred and fifty cubic centimeters of blood appears to have been adequate for this small child.

The use of Rh-negative blood for transfusion in erythroblastosis fetalis is now very largely agreed upon,^{3, 6, 7} although strong previous opinions to the contrary have been expressed.^{8, 9}

That hemolysis of the infant's blood will not alone explain the development of jaundice in erythroblastosis is clearly demonstrated by this case, as well as by others we have observed. Jaundice continued to develop after transfusion and reached its maximum on the eighth day, but during this period, no significant hemolysis took place, the red count being maintained around five million and the hemoglobin over 100 per cent. Then from the second to the sixth week there was a gradual breakdown of the transfused cells as manifested by the dropping count, followed by a slow rise as the child's own hematopoietic system gradually recovered.

The worst end result occurring in a child recovering from icterus gravis is, of course, the development of kernicterus. The hypothesis of Weiner and Brody¹⁰ concerning the pathogenesis of kernicterus is persuasive, and the plugging of small vessels in the basal ganglia by red cell agglutinates would seem to be a more potent factor in the production of brain damage than icterus per se. Certainly there are other conditions in young infants in which a marked jaundice exists over a long period of time without the occurrence of kernicterus, as, for instance, the intense icterus accompanying bile duct atresia.

Exchange transfusion appears to have a definite place in the treatment of erythroblastosis. The technique presents no great difficulties to those accustomed to transfusing small infants, and even a premature infant can withstand without signs of shock the concomitant administration and withdrawal of blood. Weiner⁴ feels that the procedure is indicated as soon as possible after birth to remove as quickly as possible the agglutinable fetal red cells. Wallerstein³ states that "such a method must seek either to remove the end products of hemolysis or to prevent their formation in excessive amounts by the removal of the Rh-positive erythrocytes before they are destroyed in large numbers by the

maternal antibody. In this way progressive hepatic damage might be arrested and the element of toxicity removed." Exchange transfusion seems to be our best method at present for accomplishing these aims.

SUMMARY

1. A case of erythroblastosis fetalis in a premature infant from a mother with sickle cell anemia is reported.
2. Treatment was by exchange transfusion with a successful end result.
3. The transfusion technique is described.
4. The rationale for the treatment of icterus gravis by exchange transfusion is briefly discussed.

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Clinical Conference

CONFERENCE AT DUKE HOSPITAL
SEPT. 18, 1947

Clinic on Poisoning

DR. G. M. CARVER, JR.—J. S., a 12-month-old boy, was admitted to Duke Hospital Sept. 8, 1947. At noon of the same day his mother noted that he was irritable but ate his lunch. Two hours later the infant vomited a small amount of blood. The hematemesis continued in progressively larger amounts. Five hours later (four hours prior to admission) the parents noted that the child had gross hematuria, a yellow tint to his skin, and was markedly restless. On admission the infant was drowsy but responded well to stimuli. The urine in the diaper was grossly bloody. The skin was markedly icteric but the sclerae were clear. There was 1+ albuminuria, a positive benzidine test, and many red blood cells in a centrifuged specimen. The white blood count was 28,000. The blood nonprotein nitrogen was 44 mg. per cent. The results of other examinations were negative.

On close questioning of the mother it was noted that the child was notorious for putting everything in his mouth. She denied the possibility of poisoning. However, that very morning they had moved into a new home, and the mother admitted that "anything could have happened."

On the suspicion that the patient had swallowed roach poison (sodium fluoride) his stomach was lavaged, and 30 c.c. calcium gluconate (10 per cent) was left in the stomach. Five cubic centimeters of 10 per cent calcium gluconate was given intravenously and 5 c.c. intramuscularly. A blood transfusion of 180 c.c. also was given. On the following morning this was repeated. The parents at this time returned with samples of roach powder that had been scattered all over the house by the departing tenants. The patient was placed on a high protein and high carbohydrate diet. He also was given sodium bicarbonate and ascorbic acid. By the second hospital day the child was eating well and did not appear ill, although the albuminuria and hematuria persisted for seven days. He was discharged on the ninth hospital day in good condition; his blood nonprotein nitrogen at that time was 34 mg. per cent.

DR. W. C. DAVISON.—This patient should be a warning to all of us to think of poisoning as the cause of bizarre symptoms. This child was seen by two other physicians, who had not considered poisoning. However, Dr. Arena not only inquired about roach poison but, when the family denied the possibility, sent them home to look for it. Fortunately, the treatment was successful, but ten hours had intervened before therapy was started, and many of the cases of fluoride poisoning are fatal in this period.

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Four hundred poisons kill over 500 American children annually. These poisons are of two groups: the first and larger in which the patient is brought to a physician because of having swallowed, inhaled, or been in contact with a known poisonous substance or been stung by some insect or snake, and being in need of immediate treatment, and the other group in which a diagnosis of poisoning is made because of certain symptoms, and for which confirmatory laboratory tests as well as specific therapy are needed, as with this patient.

The sale of lye and other poisons without a prominent label should be prohibited by law; they and all drugs should be kept away from children. Those who have swallowed lye or other poisons should be treated immediately.

DR. J. M. ARENA.—Dr. Davison has stated that over 500 American children die annually from the ingestion of poison. The number is probably much greater since many poisoning fatalities are unrecognized. However, this is only part of the picture. Many of the children who survive are left with permanent disabilities, as for example, the esophageal strictures following caustic alkali (lye) poisoning. Practically all of the deaths are caused by the ingestion of poisons in household agents. All of these can be prevented by reasonable care and precaution. All drugs and household agents containing poison should be kept away from children. The results of parents' carelessness in leaving poisons where innocent children can swallow them are truly tragic.

The history of J. S. given by Dr. Carver at least demonstrates how deceptive acute poisoning in small children can be. Here we have a one-year-old child seen by three different physicians in a period of seven hours for hematemesis. Fluoride poisoning is a very lethal type, and any appreciable amount ingested causes death within eight hours if prompt therapy is not given. The symptoms usually consist of severe hematemesis, abdominal cramps, weakness, shallow respirations, and eventually respiratory failure. Hematuria is not often mentioned, but severe damage to the tubules and glomeruli of the kidneys has been reported. Treatment consists of immediate lavage of the stomach with any soluble calcium salt (gluconate, lactate, etc.) to change the soluble sodium fluoride to the insoluble and innocuous form of calcium fluoride. Calcium should also be given intravenously and intramuscularly. Supportive treatment should be carried out as necessary.

The most frequent type of poisoning seen in this section of the country from a household agent is *caustic alkali poisoning* from the ingestion of lye. Dr. G. W. Kernodle will discuss this problem. The next most common is *kerosene poisoning*. Kerosene is often left carelessly about the home in a Coca Cola bottle in order to kindle fires, and thirsty toddlers do not hesitate to sample it. Kerosene poisoning may be followed by: (1) acute toxicity with depression, (2) severe pneumonia with fever, or (3) severe pneumonia with degenerative changes in the liver, kidneys, lungs, and heart. Treatment should consist of the cautious lavage of the stomach, trying to prevent gagging and any aspiration of the gastric contents, and leaving 30 to 60 c.c. of olive or mineral oil in the stomach. The work of Deichmann¹ and his co-workers has demonstrated that changes in the lungs can also be due to absorption from the blood stream. Un-

til recently we have cautioned against the use of gastric lavage as being dangerous. Emetics, however, should never be used in kerosene intoxication.

Reports of *aniline dye poisoning* among infants are fairly numerous. All the patients, with the exception of one, have been newborn infants poisoned by contact with diapers freshly stamped with material containing the aniline dye. One instance of paranitraniline poisoning has been reported from the ingestion of waxed crayons. Aniline dye poisoning may cause severe degrees of cyanosis due to the formation of methemoglobinemia. The infants are apathetic, gasp for air, and may develop collapse and convulsions. *Treatment*: The source of the dye should be removed immediately. Infants should be placed in an oxygen tent, and if the cyanosis is alarming, methylene blue should be given.

Mothballs composed of naphthalene are not highly toxic but may become more dangerous in the presence of oil. Naphthalene is practically insoluble in water, and most of it is passed unchanged in the feces. Treatment should consist of copious lavage with tap-water.

Deodorants are usually a solution of an aluminum salt and are practically harmless. *Depilatories* contain barium or sodium sulfide, which is fairly innocuous. However, thallium acetate, which has been used, is very toxic, causing severe gastrointestinal as well as cerebral symptoms. Treatment should consist of lavage with sodium thiosulfate, calcium by mouth, and intravenous sodium thiosulfate.

Phosphorus poisoning may occur from eating rat poison or from certain fireworks such as the giant torpedoes. Matches do not contain the dangerous form of phosphorus at the present time. The gastrointestinal symptoms are similar to those reported with sodium fluoride poisoning. Hematemesis may be severe. In the latter stages cardiac and respiratory failure develop, and sometimes delirium, coma, and death. *Treatment*: Never use oily or fatty materials such as milk, as they aid the absorption of phosphorus. Lavage promptly with 1:5,000 solution potassium permanganate to change to innocuous phosphoric acid and irrigate until the returning fluid is clear. Leave some magnesium sulfate in the stomach. Intravenous glucose and 1/6 molar lactate for acidosis should be given as necessary.

Phenolphthalein: The candy cathartics, Ex-Lax, Phenolax, etc., contain phenolphthalein, have an agreeable taste, and are frequently taken by mistake. Usually a violent catharsis is the only outcome. An eruption occasionally occurs several hours later. Hyperpraxia, hemiplegia, petechiae, ulcers in the mouth, anuria, coma, and cardiac and respiratory failure have been reported. *Treatment*: Immediate lavage or emesis; symptomatic therapy.

Strychnine poisoning, although not as common now as in the past, is still responsible for many deaths in children. Bright-colored sugar-coated cathartics and tonic tablets are responsible. Hinkle cascara tablets with strychnine sulfate (1/60 Gtt. or 0.001 Gm.), A.B.S. tablets, and many others are left carelessly about where children can get hold of them. The symptoms develop in one to three hours depending on the solubility of the tablets. The convulsions resemble those of tetanus. *Treatment*: Control the convulsions with intravenous sodium pentobarbital or Avertin by rectum. Avoid lavage until the convulsions are con-

trolled; then lavage the stomach with 1:5,000 solution potassium permanganate or tannic acid solution. Give activated charcoal in water by mouth or stomach tube. Give supportive therapy as necessary, artificial respiration, oxygen.

Stramonium poisoning (Jimson weed, thorn apple, stinkweed): All parts of the plant are poisonous but especially the seeds, which contain atropine, scopolamine, and hyoscyamine. The symptoms first noted are thirst and disturbance of vision. The pupils are widely dilated and do not react to light and accommodation. The skin is hot and dry. There is often mental confusion, convulsions, and maniacal tendencies. *Treatment*: Lavage with weak tannic acid solution (4 per cent); administer magnesium sulfate. Small doses of pilocarpine are useful. The patient should be kept in a quiet, dark room and given sedatives as necessary to control convulsions and motor activity.

Carbon tetrachloride is found in cleaning solutions as Carbona. When ingested, headache, vomiting, drowsiness, stupor, and jaundice may follow. Treatment consists of gastric lavage and calomel by mouth. Avoid alcohol. A low fat and high carbohydrate diet is advised to help prevent liver damage.

In the handling of all of these emergencies, the following should be kept in mind:

1. Identify the poison as soon as possible so that specific measures may be promptly instituted. The label on the container or household agent, if still present or legible, will give the ingredients and also the antidote to use.
2. Evacuation: Remove the bulk of the poison from the stomach by:
 - a. Gastric lavage.
 - b. Emetic (1 tablespoonful of mustard or 2 tablespoonsful of salt to glass of warm water). Emetics should never be used in kerosene and caustic alkali poisoning or if the patient is semicomatose.
3. Antidoting the residual poison not removed by gastric lavage. When a stomach tube is used, leave the antidote and other remedies in the stomach before removing the tube.
4. Antagonist when available.
5. Elimination from the system of the poison that has been absorbed.
6. Symptomatic treatment as indicated.
7. When the nature of the poison is unknown, one may safely give the following universal antidote:

Pulverized charcoal (burnt toast) 2 parts

Tannic acid (strong tea) 1 part

Magnesium oxide (milk of magnesia) 1 part

One gram of charcoal will absorb 40 mg. of phenol and over 500 mg. of strychnine. The tannic acid precipitates alkaloids, certain glucosides, and many metals, while the magnesia serves to neutralize acids.

DR. G. W. KERNODLE.—*Lyc*: I feel that most of you are familiar with lye poisoning since so many cases of stricture of the esophagus secondary to the

ingestion of caustic alkali are treated in this hospital. However, no discussion of poisons would be complete, especially in this section of the country, if lye were excluded. Commercial lye preparations contain 95 per cent sodium hydroxide, and cleansing and washing powders contain from 8 to 50 per cent of caustic alkali. Lye is still commonly used by poor people in the home manufacture of soap. The availability and widespread use of these materials account for the frequency of poisoning, especially in small children, despite the publicity which has been given concerning the dangers of lye ingestion.

If the patient is seen immediately after the ingestion of the alkali an attempt should be made to neutralize the corrosive with a weak acid such as dilute vinegar, lemon, or orange juice. Gastric lavage is not indicated, as the alkali is neutralized by gastric hydrochloric acid, and it is doubtful if much of the alkali reaches the stomach since the first swallow causes marked pain and very little is taken. Careful examination of the oral cavity should be made to see if any damage to the uvula, soft palate, or other parts of the posterior portion is evident, since this is usually an indication that some has been swallowed and that erosion of the esophageal mucosa has probably occurred. The patient should be given a sedative if restless, and the diet should consist of fluids and soft, non-irritating foods. If erosion of the esophageal mucosa is suspected, a soft rubber eyeless catheter, filled with mercury or small lead shot should be passed into the stomach at increasing intervals to help prevent the formation of a stricture. The dilatations are usually begun on the fourth day after the ingestion of the alkali and are repeated daily for two weeks, during which time the size of the catheter is gradually increased until a No. 32 or 34 is passed with ease. Dilatations are then done at less frequent intervals but continued for at least a year. A barium swallow is helpful in detecting esophageal damage and early stricture formation.

If a patient is seen several days or weeks following the ingestion of the alkali and presents the symptoms of partial esophageal obstruction, one should not pass catheters blindly but should do barium studies and esophagoscopy to determine the nature and extent of the esophageal damage. Peroral dilatations through the esophagoscope may be performed if the strictured area is single and not severe, but gastrostomy and retrograde dilatations are safer if multiple or narrow strictures are found.

Numerous articles are appearing in the various journals concerning the surgical procedures devised to correct esophageal strictures. The emphasis should be placed on early dilatations for the prevention of stricture formation.

DR. H. M. TAYLOR.—*Barbiturates* are readily absorbed from the gastrointestinal tract, the longer acting members being absorbed at a slower rate. Some are destroyed by the liver, some excreted by the kidney, and some are both partially destroyed and excreted. The excretion is fairly rapid. Where renal function is impaired the barbiturates which depend upon excretion may cause a severe depression and poisoning. In this way the ability of the liver to destroy and the kidney to excrete the barbiturate determines the duration of activity and toxicity. Death from therapeutic doses is practically unknown.

Symptoms of acute poisoning are referable largely to the nervous and cardiovascular systems. A period of excitement and hallucinations may precede the depression. Respiration is soon affected. The resulting anoxia may cause capillary dilatation and permeability and result in shock. The activity of the reflexes usually conforms to the intensity of the depression. The pupils usually react to light and may be dilated or restricted. Blood pressure falls rather late. Urine formation may be decreased or suppressed. The temperature falls; the skin is cold, moist, and cyanotic. The diagnosis is usually made from the history and physical examination. Differentiation from other central nervous system depressants or the coma due to other causes may be difficult. Identification of the drug in the gastric contents or urine is usually necessary. The prognosis is dependent upon the amount and particular barbiturate ingested, the type and promptness of therapy. The chances of survival are usually favorable after twenty-four to thirty-six hours. Death may occur as a result of paralysis of the respiratory center. *Treatment:* Gastric lavage with warm water. Emetics are of little value and may add to the depression. Potassium permanganate (1:2,000 to 1:5,000) may be effective in some instances. Magnesium sulfate left in the stomach may facilitate excretion by the intestine. Maintain respiration and blood pressure. Caffeine with sodium benzoate, ephedrine, coramine, metrazol, picrotoxin, and strychnine may be used. Give adequate fluids to maintain optimum anal excretion.

Salicylates: Salicylic acid and salicylates are readily absorbed in the gastrointestinal tract; the esters, being only slightly hydrolyzed, are largely absorbed in the ester form. Salicylic acid is readily absorbed from the skin. After absorption they are distributed throughout all tissues and fluids. They are excreted by all organs of excretion but principally by the kidney. Excretion is usually complete in a few hours but they may be demonstrated in small amounts for three or four days. Toxic reactions are usually mild but may be serious. Headache, dizziness, ringing of the ears, hearing and visual difficulties, mental confusion, sweating, thirst, nausea, and vomiting may be observed. There are skin reactions, and children may run some fever. Central excitation with restlessness, incoherent speech, mania, delirium, and hallucinations may appear. Respiration may be disturbed and resemble that observed in diabetic or renal acidosis. Depression, stupor, and coma may follow. Convulsions may be present. Death is usually due to respiratory failure. *Treatment* is largely symptomatic. Gastric lavage may be used in acute cases. The fluid and salt loss should be replaced. Intravenous glucose, shock therapy, caffeine, and ephedrine may be of value.

Mercury: Mercury is absorbed by the gastrointestinal tract, the skin, and the lungs. After absorption into the circulation it is taken up by all of the tissues but largely by the kidneys, liver, and spleen in that order. Excretion begins almost immediately after absorption and takes place largely in the kidneys and intestines. The bulk of the mercury is excreted in a few days but may be demonstrated in the urine for months. Acute poisoning is usually due to the ingestion of mercuric chloride. The mercuric (Hg^{++}) ion precipitates protein and is responsible for the ashen-gray appearance of the mouth and pharynx.

There is usually gastric pain and vomiting. It is this vomiting that often saves the patient by eliminating the mercury before adequate absorption takes place. Upon reaching the intestine the mercury produces a marked local irritation and frequently a severe bloody diarrhea. This occasionally is severe enough to cause shock and death from circulatory collapse. There is a marked stomatitis in twenty-four to thirty-six hours, foul breath, sore gums, excessive salivation, and discoloration of the gums similar to the lead line. The mercury reaches its highest concentration in the kidney, and disturbed kidney function may soon be evident. When shock has not taken place and circulation is adequate there may first be a diuresis which is followed by a more or less complete shutdown of the kidneys. Frequently the patient recovers from the local symptoms; however, systemic action starts in a few hours and may last for days with death finally ensuing. The death is largely attributed to the action of the mercury on the kidney. *Treatment:* As early as possible after the intoxication, attempt to inactivate the mercury and prevent further absorption by the administration of protein material, such as milk and eggs, and by copious gastric lavage. Sodium formaldehyde sulfoxylate may be administered in the gastric washings (250 c.c. of 5 per cent solution). Leave 250 c.c. of 5 per cent sulfoxylate in the stomach and administer intravenously 10 Gm. dissolved in 100 to 200 c.c. fluid over a period of twenty minutes. This may be repeated in four to six hours. A 1:1,000 solution of the sulfoxylate in saline may be used as a colonic irrigation. The value of the use of sodium formaldehyde sulfoxylate has been questioned, but it does no harm and may help. Maintain the normal fluid composition and promote renal action as much as possible. Give large amounts of fluid (up to 10 L. of normal saline a day) parenterally. This maintains the composition of the body fluids and produces a copious diuresis, thereby lowering the concentration of mercury in the kidney. This should continue unless considerable edema or circulatory embarrassment results. If shock develops, treat it. Sodium lactate may be used to combat the acidosis. "BAL" is being used with some success. The prognosis depends upon the amount ingested and the length of time before vomiting and treatment starts.²

DR. FREDERICK BERNHEIM.—BAL (2,3 mercaptopropanol, British Anti-Lewisite) is an example of a drug that was developed on what may be called biochemical reasoning. Sulfhydryl groups are known to be present in a number of proteins and enzymes. The enzymes containing these groups are easily inhibited by metal ions such as mercury and arsenic, and the inhibition can be reversed by cysteine or glutathione. Conversely, the enzymes can be protected from the action of the metal ions by the addition of cysteine or glutathione. It seems probable that many of the toxic effects of the metals are due to the inactivation of important enzymes such as succinoxidase and cholinesterase, which contain sulfhydryl groups. At the beginning of the war it was necessary to find an effective antidote for poison gases containing arsenic, and the biochemical knowledge available immediately suggested that a search be made for a sulfhydryl compound with an affinity for arsenic so that the arsenic would be removed from combination with the sulfhydryl groups of enzymes. The

result was BAL. The dosage recommended is 3 to 4 mg. per kilogram intramuscularly every 3 or 4 hours. This amount is about one-half the toxic dose, and consequently undesirable side effects are often encountered. These are lacrimation, salivation, nausea, vomiting, low blood pressure, and pulmonary edema. It has been suggested that previous administration of ephedrine may alleviate many of these symptoms. BAL is a good antidote for mercury, arsenic, gold, and cadmium poisoning. It is less effective for lead and silver. It will, of course, be less effective if tissue damage is extensive. It should, therefore, be given as soon as possible, and its administration should be continued until the urinary excretion of the metals is at a minimum.

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Psychologic Aspects of Pediatrics

BENZEDRINE IN BEHAVIOR DISORDERS OF CHILDREN

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FAVORABLE results have been reported in the treatment with benzedrine of a large variety of psychic disturbances in children.^{1, 2} Bradley and Bowen¹ obtained relief not only in behavior disorders of psychogenic origin but in problems of such widely different etiologies as convulsive disorders, schizoid personality, structural neurological defects, intellectual deficiency, specific reading difficulty, and postencephalitis. Seventy-two out of 100 children showed improvement. Bender² emphasizes the usefulness of benzedrine where the behavior disturbance is characterized by fear, depression, sexual tension, and hyperactivity. She observed no appreciable benefit upon the behavior of children with schizophrenia and an unfavorable effect in children with psychopathic personality.

In contrast to its stimulating effect in adults, benzedrine in children generally leads to a subdued type of behavior. Children who habitually rush about and shout become quieter, less noisy, and better controlled. They are more alert mentally and more considerate of the feelings and opinions of those around them.

In a certain number of children benzedrine results in a greater show of energy. The children are more alert, show more initiative, more aggression in competitive activities, and a greater interest in their environment.

In general, school accomplishment is more satisfactory. There is increased attention to academic work. Distractibility, fluctuations in mood, and day-dreaming are lessened. According to Bradley and Bowen³ performance in arithmetic was improved most, in spelling, least. This effect is produced by altering the emotional attitude of the child toward his intellectual tasks rather than by stimulating the higher nerve centers.

Administration.—Benzedrine is given once a day in the morning on rising. The initial dose varies from 2.5 to 10.0 mg. a day, depending on the age of the patient. It is increased every other day until a therapeutic or toxic effect results. For children requiring more than 30 mg. a day or where the morning response is not sustained, the daily dose is divided in two and is given in the morning and just before the noon meal. There is no close relationship between age and the amount of medication required.

The effects of treatment may be observed within an hour after administration. They are maximal in two to three hours and generally persist for five to eight hours. According to Bradley and Bowen¹ there is no toleration to the

drug, the effect persisting, in the large majority of instances, as long as the drug is administered.

There are no serious drawbacks to the use of benzedrine in children. Occasionally a child's behavior becomes worse. In a number of children there is insomnia, but this wears off quickly. Loss of appetite is more frequent and more persistent but is not enough ordinarily to lead to significant weight loss. Occasionally dizziness, nausea, and vomiting occur within a few hours of administration. If these symptoms persist after a day or two, the dosage must be reduced. In some instances fine tremors of the extremities are observed. They usually persist but are not marked and are not a contraindication to continued treatment.

Benzedrine is a useful aid in the treatment of disturbed children. It gives the neurotic child a feeling of well-being and temporarily allows him to feel secure. While in this frame of mind he can better face his difficulties and thereby obtain relief from inner tension and anxiety.

It is important to keep in mind that the drug is no substitute for more intensive therapy. It is useful only as an adjunct to adequate psychotherapy. It is self-evident that the drug does not remove the sources of conflict which led to the difficulty.

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3. Bradley, A., and Bowen, M.: School Performance of Children Receiving Amphetamine (Benzedrine) Sulfate, *Am. J. Orthopsychiat.* 10: 4, 1940.

The Social Aspects of Medicine

THE BRITISH MEDICAL SITUATION

[Editor's Note: The critical decision facing British physicians is of great interest and importance to American doctors, as their decision will have direct influence on the future trends of medical practice in the United States. The following discussion of the situation and problem was published in the *St. Louis Post-Dispatch*, Jan. 4, 1948. The writer, Evarts A. Graham, Jr., of the staff of the *Post-Dispatch*, has an unusual medical background for a journalist, as both his parents are physicians. His father is one of the most distinguished American surgeons and his mother has made important contributions to pharmacology. The *Journal* is indebted to the *Post-Dispatch* for permission to reprint.]

LONDON.

BRITONS will learn within the next few weeks whether their doctors are willing to give them the kind of free medical care Parliament thinks they should have. A national poll of the members of the British Medical Association will be held January 31 to determine whether the doctors wish to take part in the Labor Government's national health service plan. The plan, which was enacted in 1946 over the strenuous objections of the Medical Association, is scheduled to go into operation next July.

Under the law, every doctor and dentist is free to take part in the plan or not, as he wishes. If any considerable number of them decide to boycott the plan, however, the law will be effectively nullified because there won't be enough practitioners to go around. If, on the other hand, most doctors agree to take part, the pressure of economic necessity will compel many of the dissenters to participate.

A majority of Britain's doctors have been fighting a last-ditch battle against the law since it was enacted. Representatives of the British Medical Association and of other medical organizations, banded together in a joint negotiating committee, have been holding meetings with Minister of Health Aneurin Bevan for more than a year in an effort to reach agreement on points in dispute. Progress of the negotiations has not been made public, but it is no secret that there are still wide differences of opinion between the doctors and the Government.

By comparison with the British health service plan, the Wagner-Murray-Dingell bill to provide compulsory health insurance without interfering with private practice of medicine in the United States, is the mildest sort of proposal. American physicians who have, through the American Medical Association, attacked the health insurance plan, might well take a second look at the British plan, which has been enacted into law.

The intensity of the opposition of many doctors to the new British law, particularly the high-fee Harley Street specialists, can be judged from the final sentence of a pamphlet issued by the British Medical Association. Says the pamphlet, "the independence of medicine is at stake."

Among the sections of the act which are drawing the doctors' most concentrated fire are those which will abolish the custom of buying and selling practices, provide for state control of areas in which future doctors may practice and—the doctors think—make specialists salaried officers of regional governmental boards.

The association also objects to Bevan's proposal for payment of doctors—a system under which general practitioners would receive a salary plus a fee for

each patient treated. Parliament side-stepped the problem of the payment of doctors when it wrote the law, leaving that matter to be settled by the Minister by regulation. The doctors are violently opposed to any system which would make them "full-time salaried servants of the State," and they are fighting any introduction of the principle of paying a salary to a doctor in ordinary practice.

The British Medical Association contends that those parts of the plan will interfere unnecessarily with the freedom of the doctor, to the detriment of the medical care he is able to give, and with the doctor-patient relationship.

Proponents of the British law, some of whom agree that Parliament has saddled the plan with too many administrative bodies, reply that doctors must be directed to practice in areas where there is now insufficient medical care because there is no other way of securing enough doctors for "undesirable" places. The British Medical Association's proposed solution to the problem, extra inducements, has been tried in Britain for many years, and has been found wanting, the planners say.

SALARIES FOR DOCTORS IS A BASIC PART OF PLAN

Regarding payment of doctors, with its concomitant abolition of the institution of buying and selling good-will of practices, the plan's advocates assert that a salary must be the basic part of a doctor's remuneration, under a system in which the Government and not the patient pays for medical care, because there is no satisfactory alternative.

The system of remuneration suggested by the doctors' capitation, or payment of a fixed fee per patient treated, would lead to a production line in which quantity and not quality of treatment would be the doctor's goal, the proponents say. Good-will of practices, they add, would be an anachronism in a salaried medical service.

The new law is geared to Britain's current experiment in socialism in a democratic society. Not only the doctors but also their patients will be free to take advantage of the plan or not, as they wish. Free medical service will be provided, but if any Briton wishes to pay for his medical care and ignore the plan, he may. If he decides to use the free service provided, he may select any participating doctor he wishes. If he has no preference, he will be assigned to a doctor.

In most cases, doctors who take part in the plan may also conduct a private practice on the side. Doctors' private patients may be admitted to hospitals, all of which are to be taken over by the Government. Any patient, whether participating in the plan or not, may have a private room in a hospital if he pays for it. If the medical condition of any patient requires a private room, he will have it free.

Principal limitation on the freedom of doctors is in the law's system of "negative direction" with regard to areas in which they may practice. In the future, general practitioners who take part in the program will not be told they must practice in a given area, but areas in which they may not practice will be specified. Specialists will be attached to hospital staffs. The "negative direction" provision affects future general practitioners only—physicians now practicing in Britain may stay where they are.

An integral part of the plan is the establishment of health centers which, like Army dispensaries to soldiers, are intended to be the places where Britons will go when they want medical or dental care. In each health center will be provided facilities for doctors, both general practitioners and specialists, for dentists and for pharmacists.

The health centers will be set up by the local governments, the county councils and county borough councils, of which there are about 145 in England

and Wales. The local bodies also will make arrangements for a home nursing service, including visits by public health nurses; midwifery, and maternity and child welfare; dental service for children and expectant and nursing mothers; domestic help, when needed for medical reasons; vaccination and immunization, and ambulance services.

In addition to the local governmental bodies, hundreds of new administrative units must be established on various levels before the plan begins operating. At the insistence of the doctors, the law specifies liberal medical representation on the various bodies.

There will be a Central Health Services Council to advise the Minister, and a medical Practices Committee to decide in what areas doctors may practice. Hospitals will be administered by 15 regional hospital boards, each centered on an existing university with a school of medicine, and by subordinate hospital management committees. Patients who have no preference among doctors or dentists taking part in the plan will be assigned to a practitioner by local executive councils. A national tribunal will be established with power to remove the name of any doctor from the accredited list of those taking part in the plan.

Among other provisions of the new law, university refresher courses will be provided and a pension scheme will be established for persons providing health services under the act.

With minor exceptions, all of the medical and dental care and supplies provided will be free to all Britons. Cost, part of which will be shouldered by the national government and part by local governments, will be an estimated \$608,000,000 annually during the first few years. In addition, the Government will pay to doctors, probably when they retire from active practice, about \$264,000,000 plus interest in compensation for abolition of the selling values of their practices.

Obviously, not all of Britain's doctors are opposed to the new plan. For many of them, particularly those who have had trouble making ends meet, the plan will be a godsend. In addition, some doctors favor it because they will be able to devote most of their time to the patients who really need care, since the size of the patient's purse will not matter. Such was the experience of many doctors under Britain's "panel doctor" health insurance scheme, which has been in effect for many years to provide medical care for workers but not for their families. Such will prove to be the case, proponents of the plan are confident, when free medical care is available for all Britons.

RECOMMENDS AN INCREASE FOR THOSE PARTICIPATING

Many poorly-paid doctors support the plan because the Government is planning to give most doctors a raise. A committee composed primarily of doctors and civil servants, appointed by the Minister of Health, has recommended an average raise for general practitioners of about \$800 a year, in terms of the 1939 value of money. Sir Will Spens, master of Cambridge University's Corpus Christi College, was chairman of the committee.

"We, and not least our lay members, consider that it would be disastrous to the profession and to the public if general practice were recruited only from the less able young doctors," the committee's report stated. "Unless the financial expectations in general practice are substantially improved, the great majority of the abler men will seek to become specialists."

The Spens report, it should be emphasized, is only semi-official and does not necessarily incorporate the views of the Government. Because of the nature of the membership of the committee, and its manner of appointment, however, it is probable that the system of pay drawn up by Bevan will be based on principles and ideas expressed in the report.

Comments on Current Literature

DIARRHEA OF THE NEWBORN INFANT

IN RECENT years diarrhea of the newborn infant has become a matter of increasing concern. Conflicting views on various aspects of the problem have been expressed by different investigators in the field. A critical survey of this complex subject by Stewart H. Clifford appeared recently.¹ The serious overcrowding in the nurseries of hospitals in recent years is explained by Clifford on the basis of an increasing public demand for hospital delivery. However, while maternal mortality has reached a low figure, it remains to be seen whether the hospital or the home is the safer place for a newborn infant. Evidence submitted from New York City² has indicated a persistent upward trend in the death rate of patients in the neonatal group. This increase in neonatal mortality can be attributed in large measure to the prevalence of epidemic diarrhea of the newborn infant.

The syndrome described as epidemic diarrhea of the newborn infant is divided by Clifford into three groups according to etiology. In the first group are included disorders of bacterial origin, although the organisms isolated are frequently among those not ordinarily considered pathogenic. In this type of diarrhea the infectious agent apparently enters the nursery via an adult carrier, reaching the infant by the fecal-oral route through a break in nursery or formula-room technique. The second group includes epidemics of diarrhea in which virus etiology has been proved, or strongly suspected, and the third and largest group comprises those outbreaks in which studies have failed to demonstrate an etiological agent.

In the section dealing with epidemics of virus etiology, Clifford discusses the published reports critically and concludes that positive evidence of virus etiology has been found in only five epidemics. He emphasizes the fact that in the absence of practical methods for the isolation of virus in a given epidemic it is not possible to ascertain how many of the epidemics classed as of unknown etiology are actually of virus origin, and states that the discovery of a practical method for the isolation and identification of the virus of epidemic diarrhea would be one of the greatest advances in modern pediatrics. However, in numerous epidemics of unknown etiology, when trained investigators were called in, such incredibly poor nursery and formula-room technique was discovered that it was not necessary to resort to an unknown virus for an explanation of the epidemic. As Clifford has pointed out, "Care of the newborn must be altered so that a baby is not fed a formula containing 396,000 bacteria per cubic centimeter from a nipple covered with a pure culture of staphylococci with hands bearing *Salmonella*." When obvious breaks in technique are under control, then the importance of virus etiology may be ascertained.

Since the issue is not clear and knowledge concerning etiology is incomplete, prevention must be stressed and every precaution emphasized. Quoting Pollock,³ a hospital consultant of wide experience, Clifford agrees that "all too frequently nurseries are assigned to what might be designated as left-over space and their size is determined by the number of bassinets that can be crowded in, without any regard to spacing or the aisles between them." In accordance with the foregoing, Clifford urges that, whether in the remodeling of old hospitals or the building of new hospitals, primary attention be given to the needs of the newborn infant. The practical suggestion is offered that the number of infants assigned to a given nursery unit be restricted to the number (from six to twelve) that can be attended satisfactorily by one nurse.

Basic principles underlying the control of infection in nurseries for newborn infants are outlined. Methods designed to block airborne infection are listed: by dilution factor, by ultraviolet radiation, by the use of prophylene glycol and of oil film on floors, by the use of oil-impregnated bed clothes, etc. Elimination of infection acquired from ingestion of pathogenic organisms is accomplished most effectively by terminal-unit sterilization of the formula or fluid in the bottle with the nipple attached and covered. The blocking of infection brought about by physical contact between the infant and infected personnel or material can be accomplished by expert nursing supervision and by careful education of all personnel as to the principles and the practical aspects of this problem.

If for whatever reason diarrhea does occur in the newborn infant nursery, the following policy, as advocated by the Children's Bureau,⁴ is suggested: If one infant develops diarrhea, he should be placed immediately in an isolation nursery until the significance of the irregularity can be judged. Should two infants from the same nursery develop diarrhea, both babies must be isolated, the nursery quarantined until all contacts have been discharged, and the nursery cleaned thoroughly before any new admissions are permitted. With the declaration of quarantine a mobile nursery should be set up in an available room into which all newly delivered patients can be admitted. If three infants from the same nursery develop diarrhea, the syndrome of epidemic diarrhea is assumed, and the situation should be reported at once to the board of health. Strict adherence to this program may well limit a potential epidemic to one or two cases, while temporizing in such a situation may be disastrous.

Physicians interested in the care of infants and children are becoming increasingly aware of the importance of diarrhea in the neonatal period. Even a cursory examination of the literature indicates the great difficulties encountered in the treatment of the newborn infant with diarrhea. Mortality figures bear out this concern and emphasize the serious character of this clinical syndrome. Despite the numerous difficulties, it is heartening to know that "many large hospitals caring for thousands of babies each year have demonstrated that a strict nursery and formula-room technique can, in spite of personnel shortages and crowding, protect the newborn population from outbreaks of epidemic diarrhea."¹

RUSSELL J. BLATTNER.

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2. Frant, S., and Abramson, H.: *Epidemic Diarrhea of the Newborn*. Brennemann's Practice of Pediatrics, Hagerstown, Md., 1945, W. F. Prior Co., Inc., vol. 1, ch. 28, p. 22.
3. Pollock, H.: *Nurseries and Newborn in Hospitals*, Address Delivered Before the New England Hospital Association, Boston, March 9, 1935.
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News and Notes

The date for the 1948 annual meeting of the American Academy of Pediatrics in Atlantic City which appeared in last month's JOURNAL has been changed from early November to Saturday, November 20, through Tuesday, November 23.

Dr. Frank C. Neff of Kansas City died Dec. 3, 1947. Dr. Neff had practiced in Kansas City since 1901 and for twenty-one years had been head of the Department of Pediatrics at the University of Kansas Medical School, retiring as emeritus professor in 1947.

The annual meeting of the American Pediatric Society will be held at the Chateau Frontenac in Quebec, May 24 through May 26, 1948. It will be a joint meeting with the Canadian Society for the Study of Diseases of Children.

The Michael Reese Hospital Postgraduate School announces the following courses in Recent Advances in Pediatrics:

Section I

May 3-8, 1948 (full time)

The Full-Term and Premature Infant in Health and Disease

Section II

May 10-15, 1948 (full time)

Diagnostic and Therapeutic Measures in General Pediatrics

The tuition is \$50.00 per section. For further information and registration, address: Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th St. and Ellis Ave., Chicago 16, Ill.

The following were certified by the American Board of Pediatrics at its examination in Dallas, Texas, December, 1947:

A. L. Alfieri, 3427 Cedar Springs, Dallas, Texas.

Herbert I. Arbeiter, 5231 Hohman Ave., Hammond, Ind.

Olive Lundgren Bateman, 2426 Clinton Ave. So., Apt. E-10, Minneapolis, Minn.

Edward L. Binkley, Jr., Children's Hospital, 19th Ave. at Downing, Denver, Colo.

James F. Bosma, Dept. of Pediatrics, University Hospitals, Minneapolis 14, Minn.

Frederic Gerard Burke, Children's Hospital, 13th and W Streets, Washington, D. C.

Benjamin P. Clark, 948 Forrest Ave., Gadsden, Ala.

Michael Crofoot, 1407 Medical Arts Bldg., Omaha, Neb.

Jack Merton Docter, 738 Broadway, Seattle 22, Wash.

Herbert Burroughs Ellis, Jr., 705 East Palace Ave., Sante Fe, N. M.

Isadore M. Epstein, 525 Montana St., El Paso, Texas.

Jacob S. Fine, 4402 Lemmon Ave., Dallas, Texas.

Leo J. Flax, 858 Metropolitan Bldg., Denver 2, Colo.

Robert Lasley Forney, 1930 Truxton Ave., Bakersfield, Calif.

Louis S. Frank, 1200 North Walker, Oklahoma City, Okla.

Robert Allen Gardner, 3720 Fannin St., Houston, Texas.

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Jean Holowach, 10049 106th St., Edmonton, Alberta, Canada.
Mildred R. Jackson, 1150 North State St., Chicago, Ill.
Charles Kaplan, 1305 East 43rd St., Seattle 5, Wash.
James M. Kennedy, Jr., 602 West University, Urbana, Ill.
Isadore Lerner, 5946 West Cermak Rd., Cicero 50, Ill.
Frances Marshall Love, 3617 Maple Ave., Dallas, Texas.
Niels L. Low, 744 Main St., Racine, Wis.
George C. McCullough, Employees' Hospital, Fairfield, Ala.
Jean L. McMahon, 326 Republic Bldg., Denver, Colo.
Victor Charles McPhee, Medical Bldg., Bush and Hyde Streets, San Francisco, Calif.
Isidore Marx, 420 Lincoln Rd., Miami Beach, Fla.
Irvin H. Moore, Dep't of Pediatrics, University of Minnesota, Minneapolis, Minn.
Fe del Mundo, North General Hospital, Manila, P. I.
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Mildred A. Norval, Mayo Clinic, Rochester, Minn.
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Cathryn C. Totondo, 2005 Longest Ave., Louisville, Ky.
Herschel J. Rubin, 1619 East 15th St., Tulsa, Okla.
Henry Norris Russell, Jr., 1002 9th St., Greeley, Colo.
Mary Louise L. Scholl, Columbus Children's Hospital, Columbus, Ohio.
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Alma Marie Sullivan, 2000 Tulane Ave., New Orleans, La.
Donald Lionell Thurston, 500 South Kingshighway, St. Louis 10, Mo.
James Neal Walker, 1812 Tremont St., Fort Worth 7, Texas.
Jerome Anderson Weaver, 5 North 55th St., Birmingham 6, Ala.

Dr. Sidney Farber will deliver the sixteenth annual series of the Benjamin Knox Rachford Lectureships on Tuesday and Wednesday evenings, Feb. 3 and 4, 1948, at 8:30 P.M. in the auditorium of the Children's Hospital Clinic and Research Building in Cincinnati. The general title of his lectures will be "The Place of Pathology in the Practice of Pediatrics."

Book Reviews

Lecciones de Pediatria. From the Instituto de Pediatria y Puericultura, Buenos Aires, 1947, "El Ateneo," 477 pages.

A collection of excellent discussions of various pediatric subjects given in a course for physicians in July, 1946, by members of the staff of the institute. Among the seventeen subjects covered are infant nutrition, encephalography, the treatment of the anemias, penicillin, psychotherapy, infant surgery, and congenital heart disease. The discussions show a broad knowledge of pediatric research throughout the world. The printing is above average, and the discussions are excellently illustrated. Each discussion has a good bibliography of the subject.

Acrodynia Infantil. Juan P. Garrahan and Raphael R. L. Sampayo, Buenos Aires, 1947, "El Ateneo," 95 pages.

A monograph reviewing the etiology, symptomatology, and treatment of acrodynia. An excellent review including all the important knowledge and observations on acrodynia. Sixty-one references are included in the bibliography. The authors have nothing new to add to the theories of the etiology or the treatment of the condition.

A Study of Pediatric Nursing. National League of Nursing Education, 1947, New York, 112 pages. Price \$1.25.

The importance of the character of the nursing received by sick children in the hospital is well recognized. This study is a laudable attempt to determine the factors essential to good nursing care of children ranging in age from 2 to 13 years. It was carried out in the pediatric wards of the New York Hospital under the aegis of several sponsoring organizations and technical committees. The specific purposes were to find out what constitutes adequate nursing care of children in a specific situation, to find out how much time is required to give that care, to determine what functions can be performed by professional graduate nurses, by student nurses in training, and by trained practical nurses. A fourth purpose was to develop techniques. The method used was to have a highly qualified pediatric nurse chart, over a period of weeks, her opinion as to whether or not the physical and psychologic nursing care given by members of the three groups was satisfactory, partially satisfactory, or unsatisfactory. The results, therefore, are open to the criticism of personal opinion regardless of how objective the intentions.

Due to the nursing shortage and other factors such as a constantly fluctuating character of admissions requiring different nursing loads, the results of the study fall far short of answering the questions promulgated for the purposes of the study. There is need for a good study of pediatric nursing, and perhaps the most important result of this study is to point out the inherent difficulties to be encountered in making an objective study of the nursing needs of children. In this study the physical components of the nursing activities were found to be far more satisfactory than the psychologic components. If the report had been edited to about half of its present size, it would have been much better and would probably have received more widespread reading than it will in its present verbose form. It is a subject in which the pediatricians are decidedly interested.

B. S. V.

Editor's Column

PEDIATRIC INSTRUCTION IN THE MEDICAL SCHOOL

Included among the material recently released by the Study of Child Health Services from the recent survey of pediatric education by Dr. John Mitchell, are some interesting data on the hours used for the teaching of pediatrics in the medical schools. In fifty-eight medical schools the average number of hours used for instruction in pediatrics was 319. The high figure of 544 was reached in one school, while the lowest number of hours was 141, which is nearly 60 per cent under the average. Of the 319 "average hours," 153 were used for didactic teaching and 161 in clinical clerkships.

The increasing recognition of the importance of pediatrics in undergraduate teaching shows up strikingly when the present-day teaching hours are compared with those allotted eighteen years ago, as reported in a study of pediatric education made for the Third White House Conference on Child Health and Protection held in 1930. For this purpose we have used Dr. Mitchell's figures of "catalogue hours," which are less than the "actual hours" quoted above, as they are similar to the figures used in the White House Conference report:

HOURS IN PEDIATRICS	NUMBER OF SCHOOLS	
	1928-1929	1946-1947
400 or more	0	6
300 to 399	2	20
200 to 299	13	25
Under 200	39	8
	<hr/>	<hr/>
	54	59
Under 140	9	0

In 1928-1929, eighteen of the fifty-four medical schools offered electives in addition to the required hours. These varied so much that they cannot be utilized for comparison with the "actual hours" of Dr. Mitchell's survey, which are in excess of the "catalogue hours."

From the data on "catalogue hours" it can be calculated that the hours allotted for undergraduate instruction in pediatrics have increased over 50 per cent during the last eighteen years. With the constantly increasing developments of medical science, creating more and more pressure for curriculum time while the total hours of undergraduate instruction have not changed, this increase in pediatric hours at the expense of other branches of medical instruction shows graphically the recognition of the importance of pediatrics by medical educators.

In the 1928-1929 report, one of the conclusions and recommendations reached was that 200 hours should be the minimum time assigned to pediatrics

in the undergraduate curriculum. In the 1946-1947 year only eight of fifty-nine schools had less than 200 catalogue hours as contrasted with thirty-nine of the fifty-four in the study made eighteen years ago.

Hours in themselves are, of course, unimportant. What is important is how the hours are utilized. We can be certain, however, that this increase in teaching hours would not have taken place had there not been a coincident increase in the teaching facilities for pediatrics, and a decided improvement in the character and thoroughness of instruction by the pediatric departments.

PULMONARY INFILTRATES AND HISTOPLASMIN SENSITIVITY

The Dec. 5, 1947, issue of *Public Health Reports** contains a most unusual and interesting group of thirty-two plates of roentgenograms showing marked changes and calcification in the lungs of children with negative tuberculin sensitivity and positive histoplasmin sensitivity. Only a few years ago these roentgenograms would have been interpreted as definite proof of tuberculosis. In an editorial in the same issue on "A Problem in Mass Survey," Dr. Weber, chief of the Tuberculosis Control Division, concludes with the statement that a diagnosis of tuberculosis must be made on more evidence than is obtained from an x-ray film alone. The plates should be of value for teaching purposes.

B. S. V.

*Furcolow, M. F., Mantz, H. L., and Lewis, I.: U. S. Pub. Health Rep. 62: 1711. 1947.

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SOME mothers have the notion that babies who are fed Pet Milk, or any other evaporated milk, should be changed to another form of milk when they are taught to drink from glass or cup.

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In addition to these benefits to the baby there are advantages to the mother in the continued use of Pet Milk. Whether fed from bottle or from cup or glass it is always convenient to use, always economical—costing less generally than other forms of milk.

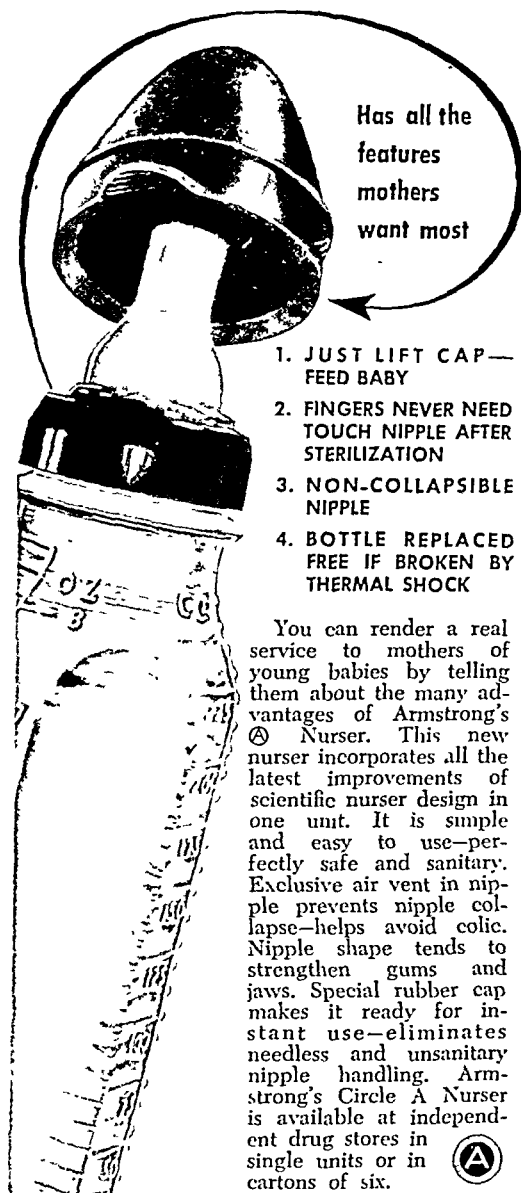
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but why wean them from Pet Milk?*

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Tales and Details



All the keys on my typewriter are stuck. My pen won't hold ink. Brother! —the first million dollars or 100 years couldn't be any harder than a columnist's first column.

(The second one better be easier than this or I'm through — 3 kids or no 3 kids!)

I'd probably never get going at all if it weren't measles season and if this column weren't about Immune Serum Globulin. This product is one of our blood fractions — HUMAN — and I write that in caps because the "human angle" in our Immune Serum Glob story is particularly important.

The fact that it's made from fresh venous — not placental — blood gives our Immune Glob three distinct advantages for passive prevention, or modification of measles:

- ✓ 1 It's water clear and hemolysis-free.
- ✓ 2 It's non-pyrogenic — causes no side reactions.
- ✓ 3 Its known and constant potency of 160 mgm. gamma globulin per cc. permits low volume, adjustable dosage.

By the way, our statistics hounds have turned up some interesting figures on measles incidence — based on a study of U.S. Public Health reported cases, 1935-45. Did you know, for instance, that 60% of all measles occur in the 12-week period, March through May?

But you're probably busy enough with those cases you have right now — and one measly column can't cover the whole story — so more next time.

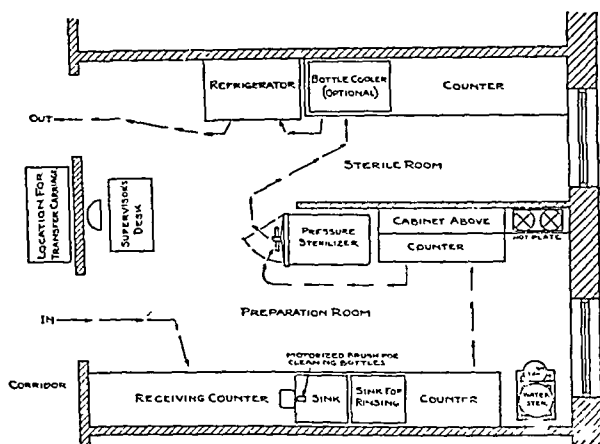
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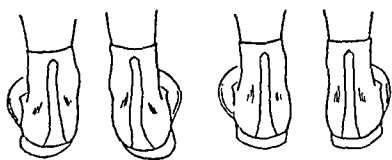
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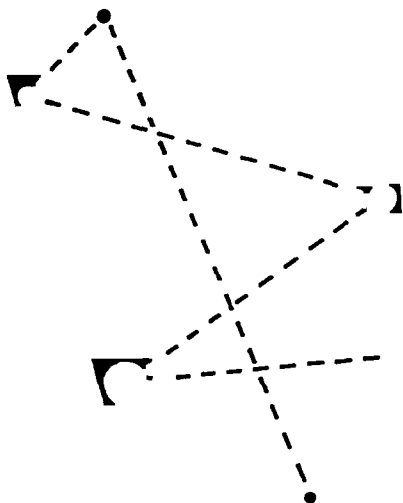
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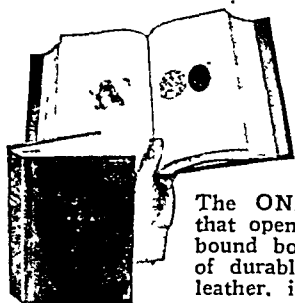


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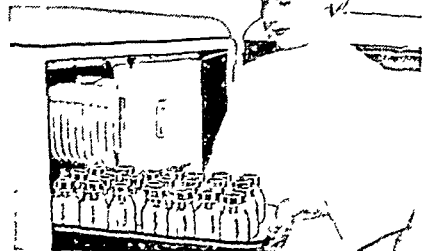


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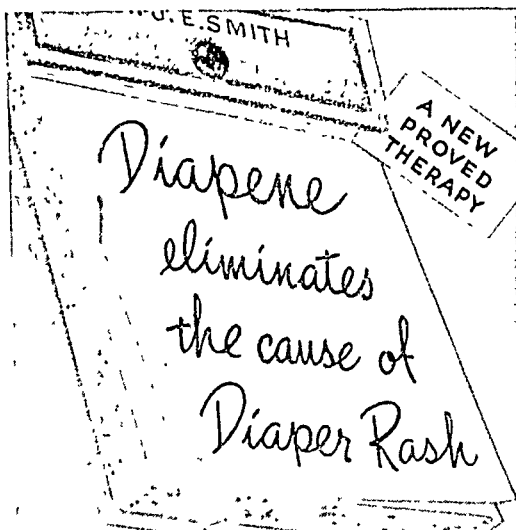
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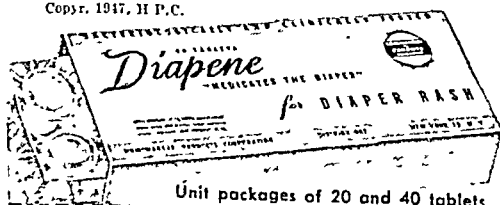
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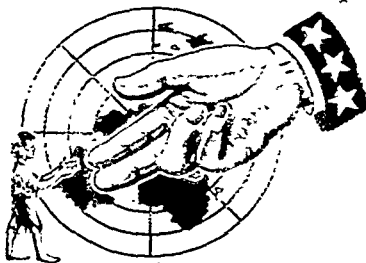
Relief of the distressed has always been a matter of American concern. In our local communities, private welfare agencies, supported by voluntary contributions, were effective in succoring needy neighbors long before the concept of public assistance became established. Similarly, a number of private American agencies, many of them representing our great religious denominations, have been carrying on works of mercy and friendship in foreign lands for generations.

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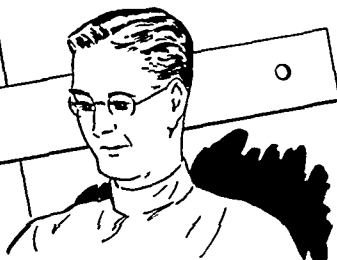
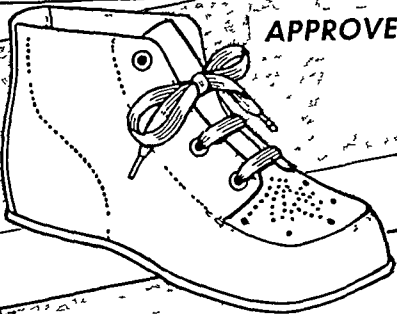
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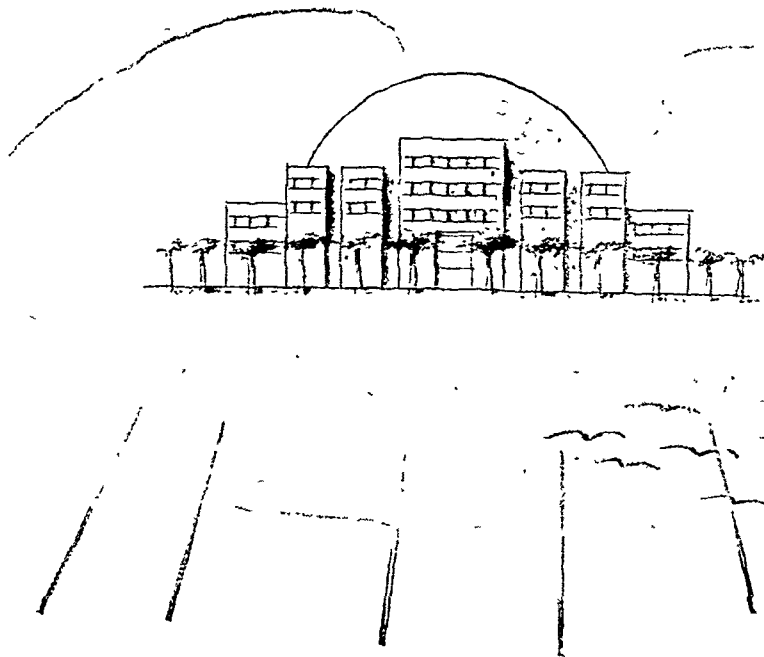
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are straight.**

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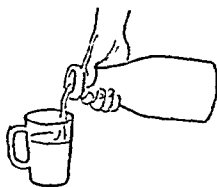
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